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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1952

ORIGINAL ARTICLES

THE EARLY DIAGNOSIS OF CANCER OF THE PANCREAS BASED ON THE CLINICAL AND PATHOLOGICAL STUDY OF ONE HUNDRED AUTOPSIED CASES*

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THE importance of early diagnosis in cancer of the pancreas has been increased since 1935 when Whipple[45] and co-workers showed that it was possible to remove the head of the pancreas and the second portion of the duodenum and have the patient survive the operation. When they made their first report the operation had been performed in 2 cases of cancer of the ampulla of Vater. Seven years later, Whipple[43] reported that he had 5 patients who survived from 5 to 28 months after this radical operation.

Many surgeons have performed the pancreaticoduodenal resection in cases of cancer of the ampulla and head of the pancreas during the past 15 years. Whipple[44] in 1949 collected statistics from 5 surgical clinics. Only 8 patients lived five years or more after the removal of a cancer of the ampulla of Vater, and only 3 survived 5 years or more when the head of the pancreas was the seat of the malignant growth. This is certainly a disappointing record. It should be pointed out, however, that this is not the fault of the surgeons, except in those cases in which the manipulation of the cancer during the operation has led to the production of metastases by cancer cells entering the lymphatics or blood vessels. There can be no doubt, however, that in most cases metastases had al-

* Read at the Sixty-fourth Annual Meeting of the American Clinical and Climatological Association, Skytop, Pennsylvania, November 6, 1951.

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ready formed at the time of operation. If cure is to be effected, the disease must be diagnosed while the neoplasm is confined to the pancreas or the ampulla. Every means of diagnosis should be employed to obtain a recognition of the disease while it is still localized; otherwise operation can do no more than prolong life and then usually for only a few months. Owing to the vagueness of the clinical picture in the early stages of pancreatic cancer, an exploratory laparotomy is indicated as soon as symptoms or signs suggestive of this disease are recognized after careful study with this possibility in mind. To delay operation until a definite diagnosis can be made will usually result in progress of the disease to such a stage that all surgery can effect is possible palliation.

We have undertaken this study with the hope of throwing additional light, if possible, on the early diagnosis of cancer of the pancreas and the ampulla. The differentiation of the two is, as Brunschwig[11] says, only "of academic interest since the treatment is the same".

Findings in 100 Cases. We have analyzed the symptoms and signs that had been present in 100 cases of cancer of the pancreas that came to autopsy in 5 hospitals. Four of these were teaching hospitals connected with medical schools.

Frequency. At the Peter Bent Brigham Hospital in Boston only 55 cases of cancer of the pancreas came to autopsy during a period of 35 years. Once, 3 years passed without the opportunity of examining pathologically a single case. This incidence is about the same in all hospitals. Hence internes rarely see enough cases to become familiar with the disease. There were 50 cases of cancer of the pancreas occurring in 7932 autopsies at the Cook County Hospital in Chicago. This was 5% of all the malignant cases. Cancer of the stomach was 4 times as frequent (Hick and Mortimer[23]).

Sex. There were 72 males and 28 females. All statistical studies show that cancer of the pancreas is 2 to 3 or more times as common in males as females. For example, of the 50 cases that came to autopsy in the Johns Hopkins Hospital 38 were males and 12 females (Duff[14]).

Age of Patients. Cancer of the pancreas is essentially a disease of later life. Only 6 of our 100 patients were under 40 years of age, and 51 were 70 or older. The oldest was 86 and the youngest 23. Two died at each of these ages. The highest incidence was in the seventies when 28 deaths occurred. In a series of 75 cases that came to autopsy at the Cook County Hospital in Chicago the largest number, 25, were between the ages of 50 and 59. Six were below the age of 40 (Arkin and Weisberg[1]). In the Hopkins series the youngest was a colored boy of 18. In the older literature collected by Oser[33], 4 were still younger. One was an infant of 7 months.

Duration of the Disease. Average duration of the disease was 7.6 months. Average duration of the symptoms prior to entering the hospital was 4.1 months. The average duration was the same, irrespective of the part of the pancreas that was the seat of the disease. On reviewing the clinical records, we found that in 55 cases the symptoms or the findings were suggestive of cancer of the pancreas. In 41 no evidence of pancreatic disease was revealed by the history, physical examination, or accessory tests at the time of admission to the hospital. In 73 cases the autopsy findings showed that cure was impossible at the time the patient was examined, either because metastases had developed or because the disease had extended

locally to such an extent as to be inoperable.

The duration of the disease from onset of symptoms to death ranged from 1 month or less to 2 years. Five lived 1 month or less; 5 from 4 to 5 months; 4 from 5 to 6 months; 11 from 6 to 10 months; 8 from 10 to 12 months; 11 from 12 to 18 months; 1 to nearly 2 years; and 1 for 2 years.

The duration of symptoms prior to entrance to the hospital was 1 month or less in 22 cases; 1 to 2 months in 17; 2 to 3 months in 17; 3 to 4 months in 12; 4 to 5 months in 8; 5 to 6 months in 7; 6 to 7 months in 3; 7 to 10 months in 3, and 10 months to 1 year in 7.

Location. The sites of the lesion were distributed as follows: Head of the pancreas 61, body 8, body and tail 7, tail 15, whole gland 8, not identified 1; total 100. In Leven's[26] series of 97 autopsied cases, the head was the seat of disease in 60, the body or tail or both in 19, the whole pancreas in 18. In Duff's[14] series of 50 cases, the head in 28, the body or tail in 19, and the whole pancreas in 3. The correspondence of the location in these 3 series is striking.

Pain. Seventy-three patients complained of pain. It was the most frequent initial symptom, occurring in 52 cases, and it was the chief symptom in 42. The pain is usually described in the textbooks as severe and deeply seated in the epigastrium and radiating to the back. This was true in only 5 of our cases. A distinctive feature of the abdominal pain in cancer of the pancreas is its persistence week after week until life's end. In the majority of cases there was nothing characteristic in the location or character of the pain. In 70 cases in which the severity and location of the pain were described in the clinical records it was continuously severe in only 18. In 52 it was moderate or mild. It was paroxysmal or occasional in some and constant in others. In 3 it occurred after meals. In one the pain came on immediately after urination or defecation and in one it was relieved by defecation. The pain was stated to be worse at night in 5, and in 3 relief was obtained by standing or walking about. In 27 of the 97 in which details are given in the clinical records there was no pain. The epigastrium was the most frequent location, as the pain was present there in 30 of our cases, but this fact is not particularly helpful in diagnosis, since in 44 cases it was present elsewhere in the abdomen or in the back or chest. In 13 cases pain was in the right upper quadrant, in 9 in the lower abdomen, and in 9 more there was generalized abdominal pain. In 9 others it was located primarily in the back, usually in the lumbar region, and in 8 cases it radiated from the abdomen to the back. Certain writers have stated that in cancer involving the body or tail of the pancreas the pain is often in the left of the abdomen. This was the location in only 4 of our cases, but in 2 of these the head of the pancreas was the portion involved.

Jaundice. Jaundice was present at some time in the course of the disease in 68 of the 100 cases. It was the initial symptom in 15 and the chief symptom in 20. In 16 cases there was painless jaundice; 32 patients did not develop jaundice. These figures correspond closely with the series of 1181 cases that Berk[5] collected from the literature. He found that 31% of the patients did not develop jaundice; we found 32% in our series of autopsied cases. As many of Berk's cases were collected from surgical records and as many instances of cancer of the pancreas are not recognized during life, we expected that our figures would show a considerably higher percentage

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that did not develop jaundice, but such was not the case.

Loss of Weight. All who have studied cancer of the pancreas agree with Bard and Pic[3], who made the first modern review of this disease, that marked loss of weight is a characteristic symptom. In 11 of our cases loss of weight was the initial symptom: 47 lost over 10 pounds in weight; 32 over 20 pounds. In addition 16 were stated to be emaciated but the amount lost was not given. In 26 without jaundice there was loss of weight. In 3 of these, the weight loss ranged from 25 to 45 pounds. In one there was a weight loss of 84 pounds before jaundice developed. Only 6 of the 100 were stated to be well nourished. The cause of the loss of weight is not known. It is not due primarily, as some have claimed, to poor absorption of food as it often occurred as an early symptom before any disturbance in digestion developed. In a case originating in the body of the pancreas a weight loss amounting to 30 pounds was the initial symptom. In our series the loss of weight in cases involving the body or tail was as great as in cancer of the head of the pancreas.

Additional Symptoms. Anorexia was present in 66 out of the 100 cases; fatigue and weakness, in 59. Nausea and vomiting were symptoms in 49 cases; constipation in 45. Diarrhea was recorded as present during the course of the disease in only 11 cases. In pancreatic insufficiency true diarrhea does not occur, as the characteristic stools are not watery but pultaceous or semisolid. In most of these cases what was termed diarrhea by the patient would doubtless have been found to have been typical of pancreatic disease, if the physicians who took the histories had made a more detailed inquiry.

Fever. Fever was recorded as present in 26 cases. In 15 the temperature was above 101°. The maximum attained was 106.5°. This occurred in 2 cases and in a third it was 106.2.° At autopsy no cause of fever was found except the cancer of the pancreas with its metastases. These findings show the error of some writers who state that the absence of fever is an aid in the differential diagnosis of cancer of the pancreas.

Leukocytosis. The frequency of leukocytosis is worthy of attention. Reference to it is rarely found in the literature, but Arkin and Weisberg[1] state that a leukocytosis above 12,000 was found in one-half of their cases in which blood counts were made, usually in those with metastases. Leven[26], on the other hand, reported counts above 8,000 in only half of his 32 cases in which the blood was examined. Blood counts were made in 69 of our cases and in 40 of these the white count was above 10,000 and in 4 additional cases between 10,000 and 11,000. In 20 it was above 15,000, in 14 above 20,000, and in 8 above 30,000.

Physical Examination of the Abdomen. A mass was felt in the upper abdomen in 38 cases out of 92. It was usually in the right upper quadrant. This was most commonly the liver which was found enlarged at autopsy in 50 cases. In a few instances the primary tumor of the pancreas was definitely palpable, but only when it had extended into neighboring organs or, as in one case, had formed a large cyst. The liver was found enlarged on palpation in 44 cases. The enlarged gallbladder was palpable on the physical examination in 15 cases and this observation was confirmed at operation or autopsy. It was found distended at autopsy in 27 cases, in 18 of these it had not been palpated. These observations confirm Courvoisier's Law that the gallbladder is dilated in obstructive jaundice caused by tumor.

Ascites. Ascites was present in no less than 24 out of 86 cases. Invasion of the portal vein or its branches was demonstrated to be the cause in some of these.

Glycosuria. At some time in the course of the disease this was present in 20 of the 100 cases. It was usually mild and transitory. Only 2 patients were definitely diabetic. According to the data of 14 authors from Mirallie[29] to Berk[5] the incidence of glycosuria was 9.4%.

Hyperglycemia. The blood sugar was determined in 18 cases. It was definitely above normal in the fasting state in 10 of these. Levy and Lichtman[27] noted the presence of hyperglycemia in 5 of the 11 cases tested. A glucose tolerance test was made in only 4 of our cases and was positive in 2.

Anemia. Among 94 cases examined there was severe anemia in 15, mild in 48, and in 31 the blood was normal.

Poor Absorption of Fat and Protein. The careful examination of the stools in the diagnostic study of pancreatic disease is most important. It is puzzling to know why the characteristic signs of pancreatic insufficiency that they exhibit have received so little attention from the authors of American text-books of medicine and of papers on the pancreas. This is not true of German writers on the pancreas. The essential methods of examination will be found clearly stated by Brugsch[10] and by Henning[22] in recent German text-books.

The bulk of the stools in pancreatic insufficiency is greater than in any other disease. This was pointed out by Oser[34] of Vienna nearly 50 years ago. The deficient digestion, he wrote, shows itself sometimes by a symptom which not seldom surprises the patient himself, and "that is the *massiveness of the stools* which appears to stand in no relation to the food consumed. I have seen a series of such cases, in which I was led by this symptom to conjecture that a pancreatic affection existed and the further course has confirmed this view." Animal experiments support these observations. A dog weighing 6,500 gm., deprived of pancreatic juice by separating the pancreas from the duodenum, passed in 4 days stools which when dried weighed 2700 gm.[38]. In the moist state this probably equalled or even exceeded the weight of the dog.

The increased bulk is due to the large amount of fat and meat that has not been absorbed in the intestine and hence is expelled. Not only are the stools voluminous, but the weight of the dried stools in occlusion of the pancreatic ducts is greater than in any other pathological condition. On the Schmidt test diet for 3 days the weight of the dried stools in health averaged 54 gm.[39]. In a case of pancreatic insufficiency reported by one of us the weight of the dried feces with the patient on the Schmidt diet was 438 gm.[36]. Even that is exceeded by 2 cases in our present series in which the weight of the dried stools, on the same diet for the same length of time, was 456 gm. in one case and 463 gm. in the other. This is the greatest on record. In no other disease has the weight of the dried stools on this diet exceeded 269 gm.[37]. In obstructive jaundice due to stone in the common duct they weigh much less. In a case on the same diet they weighed only 131 gm. To determine the important diagnostic point of bulkiness of the stools it is only necessary to collect all the stools passed in a period of 24 hours and inspect them with care.

Kuntzmann[25] (1820) appears to have been the first to associate the presence of visible fat in the stools with pancreatic disease. His report of a single

case published in an obscure journal was unknown to Richard Bright[8] who in 1833 in a paper entitled, "Cases and Observations connected with Disease of the Pancreas and Duodenum," called attention to butter-like stools as a sign of pancreatic disease. He observed and described the appearance of the stools in 3 cases: In Case 1, "The patient began to pass a quantity of yellowish fatty matter much resembling butter that had been melted and had become again solid." In Case 2, "The fatty matter formed a thick pellicle over some fluid surrounding a semi-fluid dejection and formed hard lumps as thick as a penny piece around the edges of the feces." In Case 3, "I saw the evacuations, they were abundant, of a pultaceous consistence, very deficient in bile, and most dreadfully fetid. The chamber pot was completely filled and on the surface was observed a thin scum like a thin film of grease which collected and coagulated as grease more decidedly upon the side of the vessel." In all three cases a cancer of the pancreas was found at autopsy.

Tileston[42], working at the Massachusetts General Hospital during the first decade of this century, found visible masses of fat on inspection of the stools in 5 out of 6 cases of cancer of the pancreas. For its detection it is only necessary, he wrote, "that the stools be examined frequently while the patient is on a diet fairly rich in fat (preferably in the shape of butter, cream, eggs, or olive oil) and that the stools when formed should be cut across with a knife, as the fat is sometimes in the interior of the stools when there is none on the outside."

In only 3 out of our 100 cases was the presence of visible fat on the stools noted. In the first, the report was: "Stools are very bulky, solid but unformed, pale yellow in color. One mass on the surface measuring 1 cm. in length, by 5 mm. in width and 3 mm. in thickness looks like butter. Under the microscope this is shown to be pure fat in the form of large globules." In Case 2, "Once on top of the stools some cream-like stuff consisting chiefly of large oil drops" was found. In Case 3, "Twice, although on a diet with restricted fats, there were pools of congealed fat on the top of the stools, completely soluble in ether."

There were 3 cases in which butter- or cream-like masses of fat on the stools were seen. Only 3 in 100 cases! This was the number Bright found in the few cases he had the opportunity to study, and 2 less than the single observer, Tileston, found in his series of 6 cases. What more conclusive evidence could be presented of the neglect of simple inspection of the stools in our best hospitals! Complicated laboratory procedures of little diagnostic value in cancer of the pancreas were carried out in a great many of these 100 cases, but a simple test that is pathognomonic of pancreatic disease was rarely made.

Lest it be thought that other American hospitals have made a better showing in this respect, it should be stated that in 3 papers giving careful analysis of the findings in a total of 225 cases of cancer of the pancreas that came to autopsy in the Johns Hopkins[14], Duke[9], and Cook County Hospitals[1], there is no record in the published reports of a single case in which this sign of pancreatic insufficiency was observed. But Thayer[41] of the Johns Hopkins staff reported a striking case seen in his consultation practice. The remarkable feature was that the stools "were of enormous quantity. On an ordinary diet without eating more than ordinary individuals, sometimes he passed as much as a quart

of feces; they were of remarkable appearance, semi-solid, with a gush of liquid after them at times. It did not smell like feces but like rancid butter and contained visibly large quantities of fat."

The presence of visible fat in the feces may be an early sign in cancer of the ampulla or head of the pancreas. In 2 of our cases it was the first evidence of the disease.

In pancreatic disease there is usually no visible fat on the surface of the stool when a limited amount of fat is fed, but the presence of fat, fatty acids, or soaps gives the feces a clay color. If the fatty acids or soaps are largely in the form of crystals, the color resembles that of aluminum paint or asbestos. In jaundice the color of the acholic stools is due to the presence of fat or its derivatives.

When Fitz[17] published his careful review of the literature of chronic pancreatic disease in 1903, he was able to find only 15 cases of cancer of the pancreas in which visible fat was reported as present in the stools.

In pancreatic insufficiency there are usually only 2 or 3 stools daily, unless a large amount of food is consumed. The patient may state that he had noticed cream- or butter-like material admixed with the dejections. In the first case of this kind reported in America the description of visible fat admixed with the feces was given to the physician by the patient. From this observation the diagnosis of pancreatic disease was made by Bowditch[7] and the autopsy confirmed it.

Neutral fat, fatty acids, and soaps of calcium and magnesium occur in the stools. On microscopic examination these are in the form of droplets or flakes or needle-like crystals. Stools do not appear to have been carefully studied microscopically until the eighties of the last century. Carl Gerhardt thought the bundles of needle-like crystals were tyrosin, but Müller[30], then an assistant in his clinic, discovered their true nature. Both fatty acids and soaps may appear as flakes. Only a trained examiner will recognize that these flakes are composed of fat. When a laboratory worker reports that the stools of a jaundiced patient contain "no fat" or "no excess of fat" it is evident that he does not recognize fat when present. This negative report was made on the clay-colored feces in 10 jaundiced cases in our series. Even in a case of "catarrhal jaundice," Müller[31] found 43.9% of the stool was composed of fat.

To determine even roughly the amount of fat a bit of feces should be placed on a slide and then a drop or two of 30% acetic acid added. After placing a cover slip over the preparation it should be heated to the boiling point. This procedure will convert the soap needles and flakes into droplets of fatty acid. This test was described by Adolph Schmidt nearly 50 years ago, but our study shows it is rarely used. On the other hand Sudan III is often employed to demonstrate the presence and amount of fat. This is a mistake, as it fails to stain soaps which may make up 50% or more of the fat present. If the soaps have been converted into fatty acids by boiling with acetic acid, Sudan III may then be used to advantage.

Inasmuch as a large amount of fat is found on the microscopic examination of the stools in obstructive jaundice and in sprue, the macroscopic demonstration of visible fat admixed with fecal material is of much greater diagnostic importance than the microscopic, as visible fat is observed only in pancreatic insufficiency. Müller[31] advanced the view many years ago that when the fat in the stools was found on microscopic examination to be

chiefly in the form of neutral fat it indicated a lack of pancreatic digestion, and this statement is still made in some text-books. It was later shown, however, that this simple test was valueless, as the percentage of neutral fat was not increased in many cases in which there was a complete lack of pancreatic digestion. In these cases bacterial and other enzymes had split the neutral fat into fatty acids. Müller[30] in his autobiography admits this.

Eighty-seven years ago (1864), Fles[18], a Dutch physician, wrote that he found large numbers of undigested muscle fibers in the stools in a case of extreme atrophy of the pancreas. Friedreich[19] cited this observation in his monograph on diseases of the pancreas, which was published 14 years later in von Ziemssen's "System of Medicine," which, in the English translation as well as in the original German, was widely read. He stated that this observation "is worthy of every consideration" and "the finding of undigested muscle fibers in the stools may prove of diagnostic value in pancreatic disease." That little attention was paid to Friedreich's suggestion was proved by Fitz[17] who, in a study made 30 years later, was able to find in the literature only 8 cases of proved pancreatic disease in which the stools had been carefully examined microscopically. Although 3 of the 8 patients did not pass fatty stools, undigested muscle fibers were present in every case. Thirty-nine years ago one of us wrote on the basis of personal experience that on microscopic examination of the stools "the most trustworthy sign of the lack of pancreatic juice in the intestine is the presence of large numbers of yellow muscle fibers with sharp edges and with striations well preserved[36]. Observations made since then confirm the truth of this statement. To this finding Ehrmann[15] gave the name creatorrhea. Brugsch[10] in his text-book emphasized the importance of the presence of undigested muscle fibers in the diagnosis of pancreatic disease by including a photomicrograph of such a muscle fiber with its striations well shown (see Fig. 1.). The value of this test is also recognized by French writers (Parmentier and Chabral[35]). Tileston[42] wrote in 1911 that "when pancreatic juice is deficient, it is the rule to find muscle fibers in great numbers; they are in an undigested state as shown by the preservation of the cross striations." That this simple test is not yet commonly employed in this country is indicated by the statement in a recent monograph by a leading student of pancreatic disease that "Pratt feels it safe to assert that the constant finding of large numbers of undigested muscle fibers with a normal passage of food through the intestine is diagnostic of some disease of the pancreas[6]." If the workers in a clinic where pancreatic disease has been studied with unusual care cannot speak of this test from personal knowledge, it is small wonder that it has attracted little attention in the general hospitals from which our 100 cases have been collected.

The presence or absence of undigested muscle was noted in the records of 18 of these cases; in 15 they were found present, but only occasionally in 4 of these. The amount of meat these patients received was not given. Muscle fibers were absent in only 3 cases, but 1 of the patients was on a meat-free diet except for "50 gm. of protein" twice a week. In only 3 of the positive cases was it stated that the transverse striations of the muscle fibers were preserved, and in only 2 that the edges were sharp. To perform the test properly at least 100 gm. of finely chopped beef or ham should be fed daily for 2 or 3 days. Occasionally

the muscle fibers will be abundant in one part of the stools and absent in another. As an aid in increasing the accuracy of the test a capsule containing 0.2 gm. of carmine may be given with the meat. Then the portion of the stool colored by the carmine should be examined for the undigested meat fibers.

The detection of some cases of pancreatic insufficiency requires chemical methods. A standard test diet, preferably the modification of the Schmidt diet by Nothman[32] is recommended. This is better adapted to the food habits of Americans than the original. It contains the same amounts of protein, fat, and carbohydrates. For a period of 3 days carmine or charcoal is used to demarcate the stools. After the stools are dried, their content in fat and nitrogen is determined quantitatively. This test was used in only 4 of our 100 cases, but in 2 of these it yielded positive evidence of pancreatic disease. The negative result in one case

FIG. 1.—Undigested muscle fiber in the stool in a case of obstruction of the pancreatic ducts. From Brugsch's "Lehrbuch der inneren Medizin," 6th ed., Urban and Schwarzenberg, Berlin, 1941.

was due to an accessory pancreas with a secretary duct in the wall of the duodenum.

The widespread failure to recognize the great diagnostic value of a thorough examination of the stools is the most important fact brought out by our study of 100 cases. There was no mention of the stools in 14. In 40 more no report on the microscopic examination was recorded. In 15 the microscopic examination was entirely inadequate. For example in a jaundiced patient who passed stools described as mushy and clay-colored only one was examined microscopically and this was reported "negative", although as already stated, the clay color is due to the presence of fat or its fatty acids or soaps and these may amount to 40% or more in the feces even in non-obstructive jaundice. Thirty-two stools from this same patient were tested for occult blood which was found present in all! At autopsy both the main pancreatice duct and the common bile duct were found occluded. In only 11 of our series of 100 cases was it noted that the stools were clay or tan-colored or grayish white, and in only 2 that they were bulky. In 69 an examination of the stools was either not made or was unsatisfactory. The neglect of an adequate examination of the stools was accentuated in 2 cases in which only "finger specimens" were obtained by rectal examination and these tested only for occult blood.

Occult Blood. The test for occult blood in the stools was performed in 86 cases. As it was positive in 54 (67%), it is evident that it is worthless in the differential diagnosis of cancer of the pancreas. Englemann[16] in his study of 53 autopsied cases stated that "this sign was invariably misleading in diagnosis; tentative diagnoses in these cases were limited exclusively to pathologic conditions in the gastrointestinal tract, despite negative Roentgen-ray findings."

Blood Diastase. Blood diastase was determined in 17 of the cases in our series and was increased in 7 (40%). This percentage appears to be higher than has previously been reported and furnishes evidence that calls for a wider use of the test.

In the first case it was employed in our series it gave the diagnosis of pancreatic disease in what seemed to be one of the peptic ulcer of the duodenum. The patient entered with a history of progressive weakness, attacks of dizziness, and vague epigastric discomfort.

Blood Lipase. Using the Cherry-Crandall[12] technique, Comfort and Osterberg[13] found the test positive in 40.5% of 69 cases of cancer of the head of the pancreas, and Johnson and Bockus[24] in 53.3% of their 30 cases of cancer of the pancreas. McCall and Reinhold[28] obtained an elevation of the lipase in 12 of 16 cases. Unfortunately, this test was performed in only 2 of our cases and was negative in both.

The Secretin Test. This procedure, used according to the method of Ågren and Lagerlöf[2], was performed in only 2 of the cases in our series. It showed in both a diminished volume of pancreatic juice, a low alkalinity and deficiency of trypsin, lipase, and diastase, in other words direct and definite evidence of marked pancreatic insufficiency. Hartwell[20] found the test positive in all 4 of the cases of the pancreas examined. It is not always positive as various observers have shown. Nothman[32], however, recently reported the secretin test positive in 4 out of 5 cases. No other test has yielded such definite evidence of pancreatic insufficiency in such a high percentage of cases. It is time consuming and requires the service of a

roentgenologist and a chemist. Using mecholyl instead of secretin, Bauman[4] found the pancreatic juice to be abnormal in 20 out of 22 cases of cancer of the head of the pancreas (90%). Of 6 cases of cancer of the body of the pancreas it was normal in 5.

Gastric Analysis. Heiberg[21] found that free hydrochloric acid was absent in 5 out of his 10 cases of cancer of the pancreas, but it was present in 7 of 11 cases in our series. Hence its absence would not aid in diagnosis.

Sedimentation Rate. We have data on only 10 cases, but, as the sedimentation rate of the erythrocytes was distinctly elevated in 9 of these and markedly elevated to 50 mm. or more in 1 hour in 5, it deserves to be widely employed when cancer of the pancreas is suspected. There is little reference to this test in the papers dealing with this disease, but Stern[40] reported 2 cases verified at autopsy in which the diagnosis was based on a disturbance in carbohydrate metabolism and an increased sedimentation rate.

Liver Function Tests. These were not helpful. When evidence of liver damage, as a result of obstructive jaundice was obtained, it directed attention away from the cause of the obstruction of the common bile duct, namely, the cancer of the pancreas. In one early case the examiners were so impressed by tests indicative of hepatogenous jaundice that in spite of clear-cut evidence of obstructive jaundice operation was delayed for 2 months. Even then, no metastases had formed, but local extension made cure impossible.

Roentgenological Examination. In 36 cases Roentgen-ray studies were made of the gastrointestinal tract and in 10 of these there were findings suggestive of pancreatic disease. In 3 there was a filling defect of the duodenum, in 2 evidence of obstruction of the duodenum, and in 5 evidence of an extrinsic mass displacing a portion of the stomach or duodenum.

The indirect evidence given by the Roentgen-ray has been of distinctly less value in diagnosis than the direct evidence obtained by inspection of the stools for bulkiness and free fat, the microscopic examination for muscle fibers, the chemical analysis of the stools with the patient on a test diet, the secretin test, and the demonstration of pancreatic ferments in the blood.

Operations. An exploratory laparotomy was performed in 11 cases. Two patients died on the day of operation. One died the day following. The others lived 3 to 30 days thereafter.

Cholecyst-gastrostomy was done in 3 patients. One lived 5 days, the others 6 days and 2 months. In 3 cases this operation was combined with posterior gastroenterostomy. The postoperative duration of life was 9 days, 9 months, and 11 months, respectively. Cholecyst-duodenostomy or cholecyst-jejunostomy was performed in 15 cases. Seven of these patients lived 3 to 15 months. A posterior gastroenterostomy was also done in the patient who survived 15 months.

The Whipple operation was performed in 2 cases. In one of these, death followed the second stage due to perforation of the jejunum. The other patient lived 18 months. This was the longest duration of life following discharge from the hospital of any case in our series. In all, operations were performed in 36 of the 100 cases. Ten died within the first week following the operation, 10 patients lived 1 month or more, and 9 lived 2 months or longer. Only 6 lived more than 5 months. Hemorrhage was the chief cause of death during the first weeks. Except for one case, the operations

were performed prior to the vitamin-K era.

Cancer of the pancreas is often surrounded by a zone of chronic pancreatitis, resulting probably from the occlusion of small branches of the pancreatic ducts by the neoplasm. Biopsies may reveal only the chronic pancreatitis. In one early case the first stage of the Whipple operation was performed, but as the pathologist found in the tissue removed by biopsy only chronic pancreatitis it was not completed. In a case in which pancreatico-duodenectomy was done the pathologist reported that the portion of the pancreas removed showed much fibrosis but no cancer. But when the patient died the autopsy revealed that lymph nodes about the pancreas were the seat of cancer. Bauman[4] reported a similar case.

Pathology. A detailed description of the gross appearance of the pancreas was obtained in 86 cases. In 16 of these there was marked enlargement of the organ. The largest pancreas weighed 640 gm. and measured 16 by 9 by 9 cm. The tumor involved the whole gland. No other approached this in size. The next largest weighed approximately 300 gm. The only other weights recorded in the autopsy protocols were 250 gm. and 160 gm. Most of the tumors were 6 cm. or less in diameter. In 4 instances the pancreas was stated to be small in size, and 1 was less than normal. The tumor in one case was only 1.5 cm. in diameter.

Twenty-nine of the tumors could be classified as scirrhous; none was described as soft or medullary. Among 24 cases collected by Oser[33], 19 were "fibrous" and one medullary, 3 "gelatinous" cancer, and 1 adenocarcinoma.

On the microscopic examination of the pancreatic tumor in 73 of our cases there was acini formation in 21, and duct formation in 12. In 11 cases the cells were stated to be cylindrical or cuboidal. In 12 cases it was simply stated that the tumor was an adenocarcinoma.

Venous Thrombosis. This is said to be much more frequent in cancer of the pancreas than in malignant disease of any other organ. Thrombosis or invasion of the portal vein or its branches occurred in 8 of our cases. The inferior vena cava or its branches was invaded or compressed by tumor in 3 cases.

Liver metastases occurred in 54% of the cases of cancer of the head and in 71% of the cases of cancer of the body and tail. Lung metastases occurred in 18% of the cases of cancer of the head and in 33% of the cases of cancer of the body and tail and 27% when primary in the tail alone.

Summary. 1.) The diagnosis of cancer of the pancreas must be made early, if surgery is to offer any hope of cure. The poor results that have followed the removal of the primary growth in the ampulla of Vater and pancreas are chiefly due to the formation of metastases prior to operation.

2.) If symptoms or findings are suggestive of cancer of the pancreas a diagnostic laparotomy should be performed at once. To delay until a definite diagnosis is made has proved fatal. If a patient has developed within recent weeks or months persistent, mild, moderate, or severe pain in any part of the abdomen, either paroxysmal or constant and if there has been an unaccountable loss of weight and if the physical examination and gastrointestinal Roentgen-ray studies are negative, a probable diagnosis of cancer of the pancreas is justified. In early cases of cancer of the body and tail there is no diminution of the pancreatic juice, and hence if the patient is to be saved the radical operation must be undertaken when only the

TABLE 1.—METASTASES AND INVASION OF OTHER ORGANS IN 100 CASES OF CANCER OF THE PANCREAS

Liver	62	Stomach	6
Regional lymph nodes	45	Diaphragm	6
Lungs	24	Gall bladder	6
Adrenals	10	Spleen	6
Intestines	31	Pleura	5
Peritoneum	11	Kidney	4
Retroperitoneal lymph nodes	10	Mediastinal lymph nodes	4
Mesenteric lymph nodes	10	Gastrohepatic ligament	3

Heart, omentum, inferior vena cava, urinary bladder, bone marrow, supraclavicular lymph nodes 2 each; 21 other organs and tissues, 1 each. In 14 cases there were no metastases.

TABLE 2.—RELATION OF METASTASES TO LOCATION OF THE CANCER

	Ampulla	*Head*	*Body*	*Body and Tail*	*Tail*	*Entire Gland*
No metastases	2	8	2	1	1	
Liver	2	33	7	7	7	6
Lungs		11	2	4	4	3
Pleura			1	2		2
Heart				2		
Stenosis of duodenum		6				1
Regional lymph nodes		31	2	3	4	3
Intestines		11	3	6	5	6
Peritoneum		3		4	3	1
Adrenal		5		1	1	3
Stomach		2	1	2	1	
Diaphragm		1		2	3	

symptoms just mentioned are present.

3.) Bulkiness of the stools indicates absence from the intestine of pancreatic juice, as in no other condition are the stools so massive. When collected and dried they weigh many times the normal amount.

4.) If visible fat, resembling butter or cream, is on the surface of the stools or in the surrounding fluid, it is pathognomonic of pancreatic disease. This was known to Richard Bright over 100 years ago. In order to demonstrate this evidence of pancreatic insufficiency the diet should contain a considerable amount of fat. Fat intimately mixed with the feces occurs in obstructive jaundice due to stone as a result of poor absorption of fat, caused by the absence of bile. The clay color of the stools is due to the large amount of fat, fatty acids and soap present,

and not to the absence of bile as is usually taught.

5.) The significant finding on microscopic examination is the presence of large numbers of undigested muscle fibers. Their ends are sharp or their corners square and the transverse striations are well preserved. If the results of the test are to be trustworthy, the patient should be fed daily 100 to 150 gm. of finely chopped beef or ham, given raw or lightly broiled. Unless there is an abnormally rapid passage of food through the intestine, this test, if positive, is diagnostic of pancreatic disease. The time taken by the passage of food is easily determined by giving 0.2 gm. of carmine with the meat. In obstructive jaundice due to stone the meat is well digested.

6.) The secretin test, if the technique of Ågren and Lagerlöf is followed, clearly demonstrates a deficiency of pancreatic juice if it exists.

7.) The serum lipase and serum diastase tests are usually negative in cancer of the pancreas, but if positive are diagnostic of pancreatic disease and hence should be employed whenever possible.

8.) A painless jaundice is usually due to obstruction of the common bile duct by a tumor, as has been long taught. The gallbladder is usually dilated when the obstruction is due to a cancer of the pancreas (Courvoisier's Law), but often it is not palpable, owing to the frequent enlargement of the liver in this disease.

9.) Contrary to the commonly accepted view, fever is often present in advanced cases of cancer of the pancreas. A marked leukocytosis is also of frequent occurrence in these cases.

10.) Liver function tests and the demonstration of occult blood in the stools are misleading and needlessly delay operation. Obstructive jaundice quickly produces disturbances of liver function that have led to the mistaken diagnosis of primary hepatitis.

11.) Occult blood was present in the stools of 62% of our cases of cancer of the pancreas and hence was of no value in distinguishing it from gastrointestinal disease.

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THE USE OF DEXTRAN IN THE TREATMENT OF BLOOD LOSS AND SHOCK*

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In the event of a major disaster such as an atomic explosion, many of the casualties will undoubtedly present the clinical picture of shock. By preference, treatment should consist of the rapid replenishment of their blood volume, and this is best accomplished by the transfusion of whole blood. It is doubtful that a stockpile of blood adequate to meet such an emergency could ever be maintained. Plasma obviates some of the disadvantages of blood, but the supply is short, storage difficult, and the cost great. Furthermore, the incidence of hepatitis following its use has been a justifiable cause of concern. Realization of these facts has stimulated the search for a material which could substitute for blood and plasma in expanding the intravascular fluid volume.

Previous reports from Sweden[8,9,13] and England[3] have indicated that dextran, a polymer of glucose, is a satisfactory plasma volume expander. In this country, experience with dextran has been slight, partially due to early reports of reactions following its use. A high incidence of allergic reactions following the intravenous use of a dextran of American origin was reported by Turner *et al.*[14] Lundy, using the same preparation, noted no reactions in more than 300 anesthetized patients, but did encounter reactions in a few unanesthetized subjects[12]. Goldenberg, Crane, and Popper[7] observed histopathological glomerular changes in the kidneys of dogs which had been given dextran. No reactions, however, were encountered by the Swedish and English investigators, and Lundy noted only one mild reaction in several hundred patients who received the Swedish product[11].

In regard to these conflicting reports, it should be pointed out that all dextrans are not the same. Different preparations may vary both as to molecular size, molecular weight,

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molecular shape, and the degree of branching. The initial step in preparation is the bacterial fermentation of sucrose by the organism, *Leuconostoc mesenteroides*. The product of this is a viscous mass consisting of very large dextran molecules unsuitable for use in man. This material is next subjected to partial acid hydrolysis, which splits the molecules into units of smaller size. There still remains, however, a wide range of molecular size, which can be narrowed appreciably by a process of alcohol fractionation. It is not known whether refinements in the preparation of partially hydrolyzed dextran, eliminating the very large molecules, and resulting in a more uniform mixture of lower molecular weight, have anything to do with avoiding untoward reactions in man. Some dextran preparations have caused reactions, while others have not; and until the mechanism of these reactions has been determined, it is necessary to judge each preparation on its own merits[1].

The American dextran* used in this study has been fractionated to an average molecular size of about 70,000, comparable to that of human albumin. This material has been administered to more than 100 patients suffering from a variety of acute and chronic diseases without encountering any untoward reactions or evidence of impairment of renal or hepatic function[1]. It expands plasma volume for 6 to 24 hours after the infusion. From 30 to 50% of the amount given is excreted in the urine during the next 72 hours[1]. The fate of the remainder is not clearly understood, but evidence is accumulating to indicate that it is broken down to glucose and metabolized[4]. Dextran has been used without difficulty after being stored for as long as a year at room temperature. The present report is concerned with its safety and effectiveness in the treatment of experimental acute blood loss and in patients with various types of clinical shock.

Methods. A 6% solution of dextran in physiologic saline solution, a concentration which approximates the colloid osmotic pressure of plasma, has been used in these studies. As a preliminary investigation, the circulatory changes occurring with experimental blood loss and dextran replacement were observed in 5 normal, healthy men. The pulmonary artery was catheterized by the usual technique,[15] and an indwelling needle was placed in a convenient peripheral artery. Pressures were measured by Sanborn electromanometers and recorded together with a simultaneous electrocardiographic lead on a direct writing, multichannel recorder. Cardiac output was determined by both the direct Fick principle and the dye-injection method of Stewart and Hamilton[10]. Dye injections were made through the catheter into the pulmonary artery as suggested by Ebert[6]. The so-called "pulmonary blood volume" was calculated from the dye output and the mean circulation time. A 10-minute arterial sample was collected for estimation of the general blood volume. After suitable control determinations were made, the subjects were bled at an average rate of 45 cc. per minute, the total amount varying from 450 to 900 cc. The above observations were then repeated. The subjects were next given an infusion of 500 cc. of dextran solution at an average rate of 28 cc. per minute. At the conclusion of the infusion, the observations were repeated a third time. In all except subject 5, the cardiac output was again determined 40 to 60 minutes later.

The remainder of this report consists of clinical observations made on 52 patients suffering from various types of shock and treated with a 6% solution of dextran. Either 500 or 1000 cc. were given, depending on the condition of the patient. All of these patients presented the clinical picture of shock, and had a systolic blood pressure less than 90 mm. of Hg. A few had received infusions of saline or glucose solutions prior to dextran therapy but without a lasting effect on their blood pressure or clinical state. Blood pressure, pulse rate, skin color, and body temperature were determined before and at frequent intervals during and after therapy. In approximately one-half of the cases, multiple blood samples were collected before and

* "Expandex," kindly supplied by Commercial Solvents Corp., Terre Haute, Ind.

TABLE 1.—HEMODYNAMIC EFFECTS OF BLOOD LOSS AND DEXTRAN REPLACEMENT

Subj.	Time of Observ.	Age (yr.)	Surface Area (sq. m.)	Pulse Rate (beats/min.)	Hematocrit Reading	Systemic Arterial Pressure (mm. Hg)			Mean Pulmonary Arterial Pressure (mm. Hg)	Oxygen Consumption (cc./sq. m. /min.)	Arterial Oxygen Capacity (cc./100 cc.)	Arterial Oxygen Content (cc./100 cc.)	Venous Oxygen Content (cc./100 cc.)	A-V Oxygen Difference (cc./100) cc.	Cardiac Index (Fick) (L./min. /m²)	Mean Circ. Time (sec.)	General Blood Volume (cc.)	Pulmonary Blood Volume (cc.)	Cardiac Index (dye) (L./min. /m²)
						Sys.	Dia.	M.											
1	Control	24	1.66	60	40.4	130	85	107	14.0	139	18.1	17.3	12.8	4.5	3.1	13.3	4945	1042	2.8
	Phlebotomy, 450 cc.			65	39.2	125	80	97	10.0	154		16.9	12.3	4.6	3.4	13.4	4548	916	2.5
	Dextran, 500 cc.			65	34.7	135	90	105	16.5	150		14.5	10.7	3.8	3.9	13.6	5109	1077	2.9
	45 min. after dextran			65	34.7	145	100	115	16.0	155		14.7	10.4	4.3	3.6				
2	Control	20	2.04	75	38.1	122	75	87	14.0	136	16.6	15.7	12.2	3.5	3.9	9.2	5816	1042	3.3
	Phlebotomy, 900 cc.			85	35.1	100	60	75	11.0	151		14.8	10.7	4.1	3.6	9.4	5141	816	2.6
	Dextran			85	30.9	135	82	100	16.0	149		13.3	10.4	2.9	5.1	9.6	5569	1265	3.9
	40 min. after dextran			85	30.8	135	75	100	16.0	161		13.0	10.1	2.9	5.5				
3	Control	22	1.81	58	47.4	140	80	100	16.0	139	20.2	19.2	15.6	3.6	3.9				
	Phlebotomy, 500 cc.			65	46.4	150	82	102	10.0	136		18.9	15.4	3.5	3.8	12.0	5164	1000	2.8
	Dextran, 500 cc.			65	40.8	155	87	110	16.0	155		16.7	13.4	3.3	4.7	11.2	5839	1064	3.2
	60 min. after dextran			64		147	90	112	16.0	140		16.6	13.1	3.5	4.0				
4	Control	42	1.96	85	44.9	125	82	105	17.5	110	18.4	17.1	13.7	3.4	3.3				
	Phlebotomy, 500 cc.			85	44.3	125	84	107	11.5	112		16.5	12.5	4.0	2.8	6.8	4488	815	3.7
	Dextran, 500 cc.			90	36.7	125	83	110	18.0	110		14.1	11.0	3.1	3.5	7.3	4731	803	3.4
	60 min. after dextran			85					18.0	108	15.4	14.5	10.6	3.9	2.8				
5	Control	19	1.81	75	40.5	137	75	87	13.0	141	17.0	15.7	11.8	3.9	3.0	13.7	4835	1097	2.7
	Phlebotomy			75	40.6	120	65	85	5.5	145	16.7	15.5	11.0	4.5	3.3	12.8	4507	1068	2.8
	Dextran, 500 cc.			75	33.3	147	67	95	16.0	149	14.0	11.5	7.9	3.6	4.1	11.9	4862	1169	3.3
Av.	Control		1.86	71	42.3	131	79	97	14.9	133	18.1	17.0	13.2	3.8	3.4	12.1	5199	1060	2.9
	Phlebotomy			75	41.1	124	74	93	9.6	140		16.5	12.4	4.1	3.4	10.9	4769	923	2.9
	Dextran			76	35.3	139	82	104	16.5	143		14.0	10.7	3.3	4.3	0.7	5222	1076	3.3

after dextran for determination of the hematocrit reading, hemoglobin concentration, and dextran level[2]. All patients were followed until their clinical state had stabilized.

Results. The hemodynamic effects of moderate experimental blood loss and replacement with dextran solution are recorded in Table 1. None of the subjects was bled sufficiently to produce shock. As expected, immediately after acute blood loss the hematocrit reading changed only slightly. The systemic arterial pressure was significantly reduced only in subject 2, who was bled 900 cc. The degree of hemorrhage carried out in these patients did not appreciably alter the cardiac output. The average total blood volume decreased 12% and the so-called "pulmonary blood volume" underwent a similar decline. The average fall in mean pulmonary arterial pressure was 36%. The infusion of dextran solution returned these hemodynamic changes to or above normal, except for the evidence of hemodilution, which was indicated by the 17% fall in hematocrit reading. Systemic and pulmonary arterial pressures returned to values slightly higher than the control level. Cardiac output was increased an average of 26% immediately following the dextran infusion. Despite the fact that the same degree of hemodilution was present 40 to 60 minutes after the infusion, the cardiac output at that time had in most instances returned toward the control level. The general blood volume and "pulmonary blood volume" returned to their original values.

The results obtained in patients with clinical shock treated with dextran are indicated in Table 2 where they are listed according to the type of injury or disease. A *good result* is defined as one in which there was a prompt return of the blood pressure to normal with disappearance of the clinical signs of shock. Ten of these patients subsequently received blood transfusions in preparation for or during surgical procedures, or because of continued bleeding. In none of these patients did high dextran blood levels following therapy interfere with the typing or cross-matching of blood. A *temporary result* indicates improvement in the clinical state following dextran, but subsequent relapse into shock within the next few hours. Those patients listed as showing *no response* obtained no obvious benefit from dextran. Of the 8 patients showing a poor response to dextran, all but one showed similar unsatisfactory re-

TABLE 2.—SUMMARY OF PATIENTS WITH SHOCK TREATED BY DEXTRAN INFUSION

	Response		
Injury or Disease	*Good*	*Temporary*	*None*
1. Lacerations	13	0	0
2. Skeletal trauma	6	0	1
3. Penetrating chest wounds	7	0	0
4. Penetrating abdominal wounds	5	0	0
5. Gastrointestinal hemorrhage	3	0	0
6. Cerebral trauma	2	3	2
7. Infection	1	2	0
8. Diabetic acidosis, burns, etc.	7	0	0
Totals	44	5	3

sponses to blood and other types of therapy and eventually succumbed to their injury or disease.

As can be seen from the table, the greatest number of patients treated were suffering from shock due to blood loss with varying degrees of trauma, and in these patients the most satisfying results were obtained. Poorest results were seen in those patients with cerebral damage or overwhelming infections, conditions which are frequently unresponsive to any type of therapy. Of the total of 52 patients treated, good results were obtained in 44, 5 patients showed only temporary improvement, and 3 failed to respond at all.

Hemodilution following dextran was demonstrated by a fall in hematocrit reading and hemoglobin concentration. Determination of blood dextran levels were carried out in a majority of the patients observed. The level attained varied from 450 to 2500 mg. per 100 cc. of blood. The absolute height reached appeared to depend on such factors as the size of the patient, the amount of blood lost, and the amount of dextran infused. The peak value was demonstrated almost immediately following the completion of the dextran infusion and later blood samples showed a gradual diminution.

No untoward side effects or reactions were observed in the patients reported here as a result of the dextran infusion.

Discussion. The results in the normal individuals show the ability of dextran to re-expand circulating fluid volume following experimental blood loss. Although it was not technically possible to determine the general blood volume over a longer period of time, there was evidence that hemodilution persisted through the 40 to 60 minute post-infusion observation period. It has been shown in other normal individuals that the hemodilution persists for 6 to 24 hours[1]. The average increase in plasma volume following the infusion was 453 cc., or 15.1 cc. per gram of dextran infused.

The fall in pulmonary arterial pressure as a result of the hemorrhage and the brisk return to normal during the dextran infusion are the results of volume changes within the pulmonary vascular bed, a phenomenon which has been described in a previous report from this laboratory[5]. Although there was some individual variation, the average change in the so-called "pulmonary blood volume" was proportionate to the change in general blood volume. The increased cardiac output following dextran infusion has been observed by others to occur in normal individuals without previous blood loss[16]. The cardiac output in most cases had returned toward normal within an hour, even though hemodilution persisted.

A variety of clinical conditions resulting in shock were treated with dextran. The most dramatic effects were observed when relatively uncomplicated but severe blood loss had occurred. Seven patients with penetrating chest wounds were treated and responded similarly to those with injuries to other parts of the body. It was the impression of those observing the action of dextran that it performed as well as plasma. The convenience of administration was an especially desirable feature in a busy emergency room, and the lasting effect was in striking contrast to the evanescent action of saline solution.

It is not our intent to suggest that dextran can ever supplant whole blood, which is still the most efficacious agent in the treatment of hemorrhagic shock. In ordinary civilian medical practice today, blood is usually available and will continue to be the pre-

ferred agent. In the event that blood is not readily available, however, it would be desirable to have a means of treating the patient's shock in order that he may survive until definitive treatment may be given. The ease with which dextran can be stored and administered and its freedom from harmful reactions would seem to make it ideally suited to this purpose. The elimination of human blood donors as a source of supply is its chief advantage over plasma and concentrated human albumin. In addition, the danger of transmitting serum hepatitis to recipients is averted. It is possible that by alleviating shock with an early dextran infusion prior to administration of whole blood one would also lessen the danger of lower nephron nephrosis occurring as a complication of shock and transfusion.

Summary. 1. A solution of dextran, a glucose polymer, has been given to 5 normal individuals previously subjected to experimental blood loss of from 450 to 900 cc., and to 52 patients suffering from clinical shock.

2. The use of dextran following experimental blood loss resulted in hemodilution and an increase in the circulating plasma volume. In the treatment of shock due to blood loss, trauma, and dehydration, dextran brought about satisfactory clinical improvement. Results were poor in those patients with cerebral trauma or infection, even though satisfactory hemodilution occurred. In general, the therapeutic results were essentially the same as might have been expected from plasma.

3. Dextran appears to be a satisfactory plasma volume expander offering advantages of large scale production, storage stability, and convenient, reaction-free use in clinical practice.

The authors wish to express their gratitude to Mr. Earnest Atkins, Mr. Richard Dodelin, Mr. Ira Ferguson, and Mr. F. E. Montague, students of Emory University School of Medicine, without whose aid the clinical data reported in this paper could not have been obtained.

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STREPTOMYCIN THERAPY IN PULMONARY TUBERCULOSIS
A CONTROLLED STUDY*

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THE clinical response of pulmonary tuberculosis to streptomycin is well known and has been widely reported by many investigators[1,2,3]. However, the character of the disease has made it extremely difficult to carry out adequately controlled studies among sanatorium patients. Because of this fact, the majority of the clinical reports of streptomycin therapy in pulmonary tuberculosis have not been of this nature. It might be stated that such a study probably could not be repeated in any tuberculosis sanatorium today since a very large number of patients admitted have previously received streptomycin. In addition, we feel that one could not at this time justifiably withhold the antibiotic from significantly large numbers of patients. For these reasons, it is felt that our experiences in a controlled study are worth reporting.

Material and Methods. The patients used for this study were chosen from routine admissions to Robert Koch Hospital, the St. Louis Municipal Tuberculosis Sanatorium. Only patients with positive sputum were considered. Automatically excluded from consideration were those who had minimal lesions by the N.T.A. standards and those who were classified as terminal and could not be expected to benefit from antimicrobial therapy. When deemed suitable for the project, each patient was carefully observed for one week, preliminary roentgenograms were taken, and all information was then forwarded to the Selection Panel, where, on an impartial basis, each was designated for the streptomycin or control group. Of those submitted, 85 were accepted for the study, 42 to be treated and 43 for control. There were 23 males treated and 22 male controls, 19 females treated and 21 female controls. Twenty-three white patients, 18 Negroes, and 1 Chinese were treated. Seventeen white patients and 26 Negroes constituted the control group. Six of the patients who were treated and 9 of the controls were under 25 years of age. Twenty-three of the treated patients varied from 26 to 45 years of age, and 22 of the controls were between 26 and 45. Of those over 46, there were 13 treated cases and 12 controls. The majority exhibited far advanced tuberculosis with cavitation. However, 8 control and 7 treated patients were classified as moderately advanced and 4 control and 9 treated subjects had no cavity demonstrable on roentgenograms. Each patient in the streptomycin group received 0.1 gm. per 11 pounds of body weight daily with a maximum dose of 1.5 gm. The total daily dose was divided equally and given at 8-hour intervals for a period of 91 consecutive days. When indicated, all the various forms of collapse therapy were instituted in patients in both categories. Every patient on the project was given a tuberculin test. Periodic follow-up observations were made at 3-month intervals

* This investigation was supported (in part) by a research grant from the National Institute of Health, Public Health Service.

for 12 months. These included body weights, temperature studies, sputum studies, roentgenograms, blood urea nitrogen determinations, complete blood counts, urinalyses, caloric sensitivities and audiograms. Cultures and guinea pig inoculations of gastric washings were done whenever routine sputum examinations were negative. Cultures on Petragnani's medium were forwarded to Dr. Guy P. Youmans, of Northwestern University, for sensitivity tests, at the start of the study and subsequently during the 5th and 9th weeks of treatment, and the 1st, 14th, 22nd, and 40th weeks after completion of streptomycin therapy.

mycin and control group at the beginning and end of a year's observation showed a definite advantage in favor of the streptomycin treated patients (Fig. 1).

Temperature Study. Temperature studies showed both groups to be comparable in the pre-treatment period. Immediately after streptomycin therapy there was a marked increase in the afebrile group, and a definite decrease in the slightly febrile and feb-

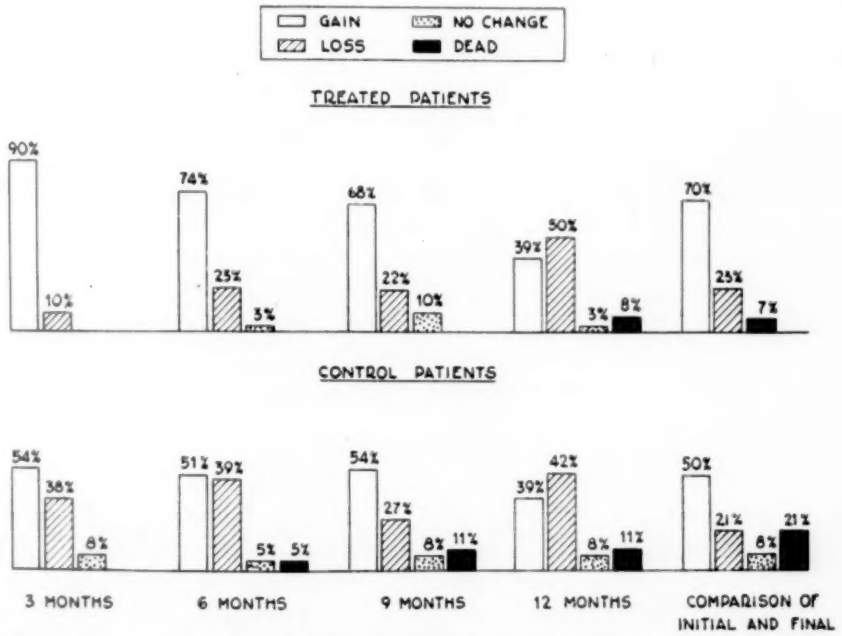

FIG. 1.—Body weights in control and streptomycin treated groups at 3-mo. intervals in a year's study.

Results. CLINICAL STUDY. *Body Weight.* A comparison of body weights after the first 3 months revealed a decided increase in weight in the streptomycin group, to a lesser extent in the control group. At the end of 6 months, this advantage was still maintained. After the 9 and 12 months' period the 2 groups approximated each other. A comparison of the streptorile groups, as compared to the control patients. Subsequently, there was little significant change in the treated cases. In the control group, there was a gradual increase in the number of afebrile cases, and a gradual decrease in the markedly febrile cases, both reaching a maximum at the end of a year. The number of slightly febrile

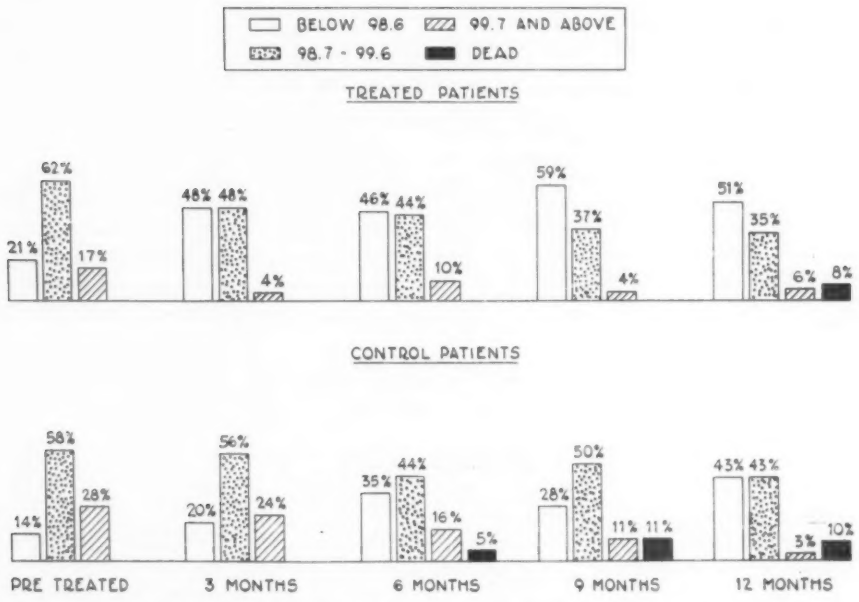

FIG. 2.—Temperature studies in control and streptomycin treated groups at 3-mo. intervals in a year's study.

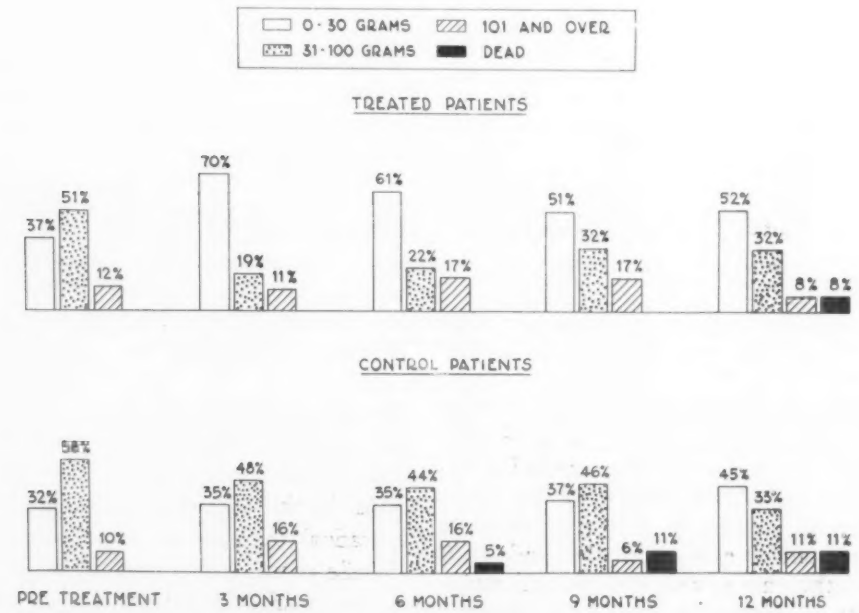

FIG. 3.—Sputum weights (gm./24 hr.) in control and streptomycin treated groups at 3-mo. intervals in a year's study.

cases decreased but little throughout the study (Fig. 2).

Sputum Weight. Sputum weights in grams per 24 hr. in the 2 groups were approximately the same at the start of therapy. The streptomycin group showed a marked drop in sputum weight at the end of 3 mo., a definite advantage over the control group. At 6 and 9 mo. the streptomycin treated group maintained its advantage, although to a lesser extent. In the control group, there was a very gradual decrease in sputum weight so that at the end of the year the number of patients who produced little or no sputum almost approximated the number in the treated group (Fig. 3).

ROENTGENOLOGICAL STUDY. An evaluation of the changes in the roentgenograms was made at 3 mo.-intervals throughout the period of study. It should be emphasized that each roentgenogram was compared with that made at the end of the immediate preceding period. The most marked improvement occurred at the end of the first 3 mo. in the streptomycin treated group. This improvement continued during the 2nd and 3rd 3 mo. In the 4th period, there was only slight improvement in the treated patients. The control group showed a moderate but constant number of improving cases throughout the study (Fig. 4).

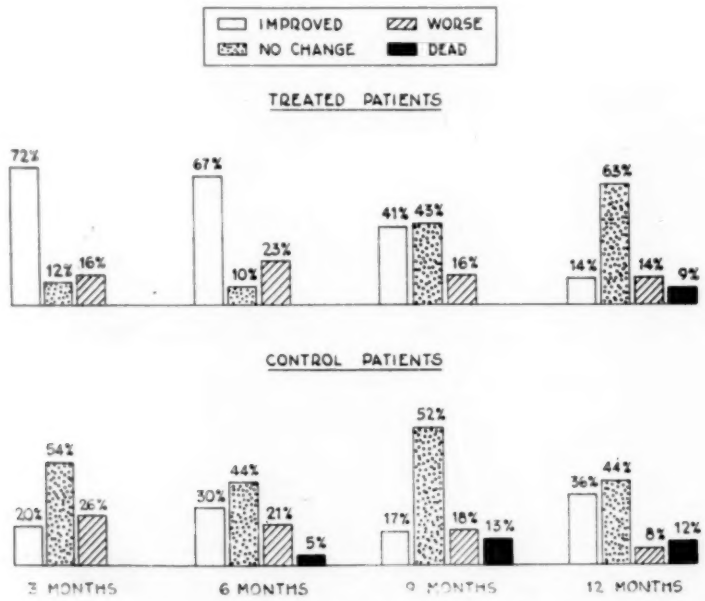

FIG. 4.—Changes in roentgenograms in control and streptomycin treated groups at 3-mo. intervals in a year's study.

Comparison was made of the roentgenograms of the 2 groups 1 year after the beginning of streptomycin therapy. The streptomycin treated group demonstrated decided advantage over the control group, 77% of the cases showing improvement as compared to 31% of the controls. Only 15% of the treated patients were worse, as compared to 41% of the control patients (Fig. 5).

BACTERIOLOGICAL STUDY. *Sputum Conversion.* Sputum conversions in the 2 groups were determined at 3 mo.-intervals. The streptomycin group showed greatest advantage after the first 3 mo. period. There was a decrease in conversions during the 2nd period, a rise during the 3rd period, and no significant change during the 4th period. The control group showed a gradual increase in conversions after the first period, reaching its maximum at the end of 12 mo., but did not reach the level of the streptomycin group at any time (Fig. 6).

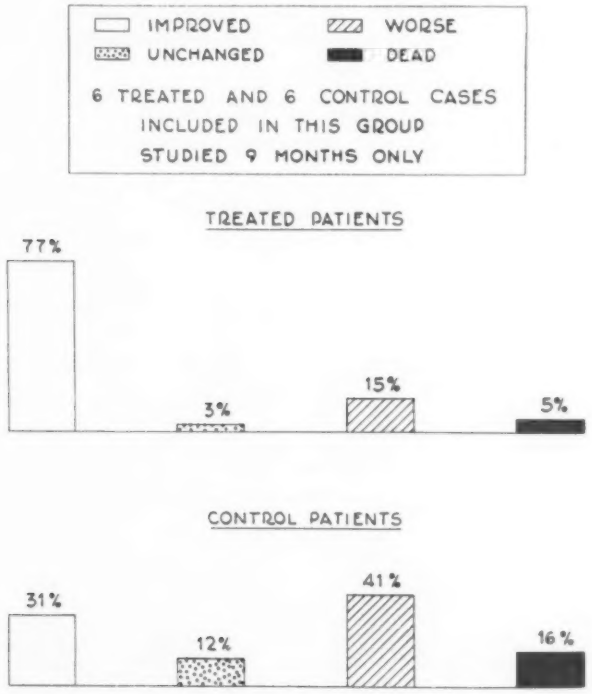

FIG. 5.—Changes in roentgenograms in control and streptomycin treated groups 1 yr. after beginning therapy.

Sensitivity Study. All cultures were sensitive to 3 micrograms (mcg.) of streptomycin per cc. of culture medium prior to the administration of the drug. Resistance appeared as early as 5 weeks after beginning of therapy in 15% of the cultures; it gradually increased to 39% after 9 weeks and to 46% at the end of therapy. Without further treatment, there was a continued increase in the number of resistant cultures, reaching 100% 12 mo. after the start of streptomycin therapy.* It must be understood that these percentages are based upon the obtainable cultures and not upon the total number of patients at any one period (Fig. 7).

TOXICITY STUDY. Eosinophilia was present in 56% of the treated group but was of no significance in the re-

* In one instance a duplicate culture at this period was reported as showing sensitive organisms.

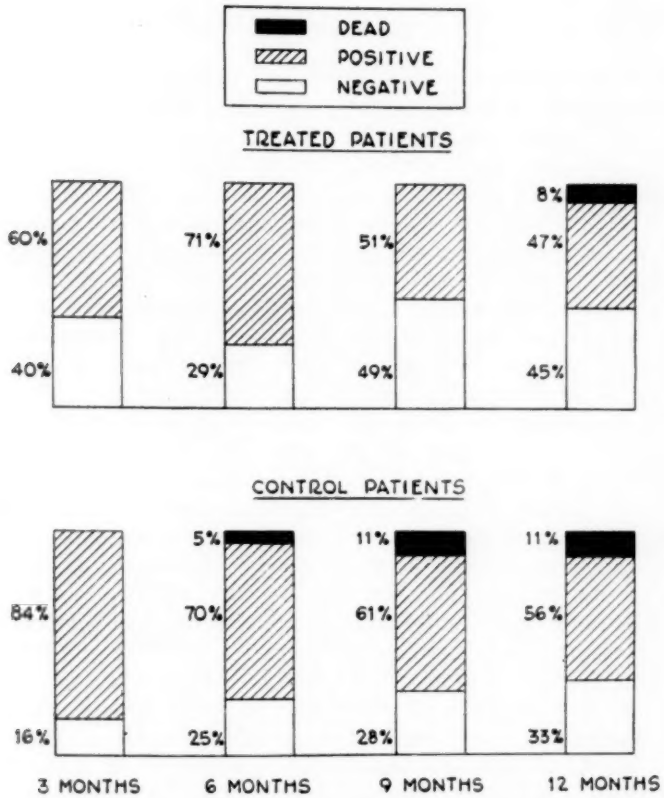

FIG. 6.—Sputum conversions in control and streptomycin treated groups at 3-mo. intervals in a year's study.

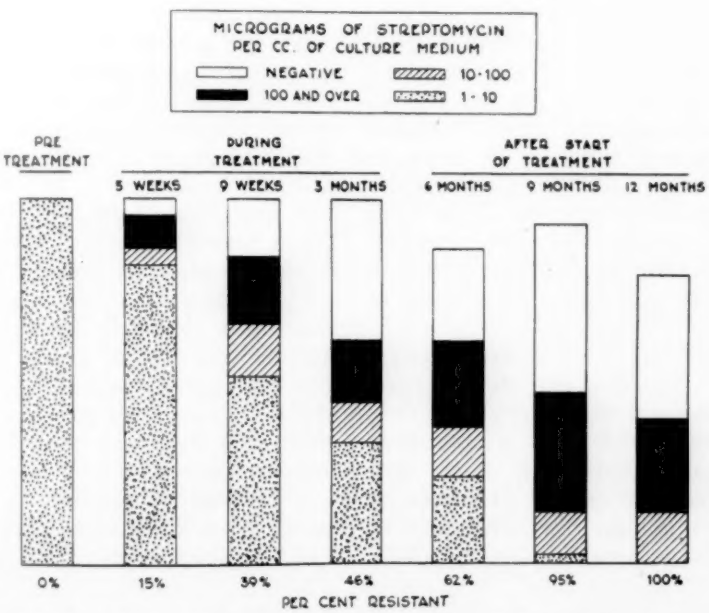

FIG. 7.—Studies of sensitivity to streptomycin before and during a year's treatment.

sults obtained. Dermatitis was present in 4%. Renal damage was negligible. The chief toxic effect was on the 8th nerve. Thirty-eight percent of all treated patients showed some form of vestibular damage, usually of a minor nature. All of the patients showed an almost complete compensation even after permanent damage to the vestibular system. Tinnitus occurred in 4 patients. Three patients had partial deafness from which they recovered.

Discussion. This study confirms the generally accepted belief that streptomycin is a valuable therapeutic adjunct in the treatment of pulmonary tuberculosis. Analysis of our results shows a greater improvement in the streptomycin group in respect to body weight, temperature, sputum weight, sputum conversions, and roentgenographic changes. This difference is quite striking at the end of 3 mo. The advantage continues to be marked at the end of 6 and to a somewhat lesser extent at the end of 9 mo. At the end of 12 mo., 9 mo. after cessation of therapy, the streptomycin treated patients maintain a distinct advantage over the control patients.

Comparison of the roentgenographic changes at the end of 1 year shows marked improvement in the treated groups, which is striking as compared to the control group. Over twice as many of the treated patients show some degree of improvement as compared to the controls. The extent of improvement in the streptomycin group is frequently dramatic, particularly at the end of therapy.

The percentage of sputum conversions of streptomycin therapy has been disappointing. There is a definite advantage in the streptomycin treated cases, particularly at the end of the treatment period. However, at the end of a year, this advantage in sputum conversions becomes relatively small, the control group showing an increasing percentage of conversions at each period. It seems clear that reliance cannot be placed on streptomycin alone as a mechanism for sputum conversions, and that sanatorium care in conjunction with the usual surgical measures for well over 12 mo. is necessary for conversion of most cases.

After 3 mo. of streptomycin therapy, approximately ½ of the cultures were either moderately or strongly resistant. At the end of 1 year, there were only 13 available cultures, all of which were resistant. Of these, 8 had been sensitive at the end of streptomycin therapy. One can only speculate on the resistance of the organisms which the "negative" patients may still harbor. It is probable that many of them may still be sensitive. We have observed 1 patient who is included in the "negative" group who recently has developed a positive sputum long after the termination of this study. Sensitivity studies of these organisms show them to be sensitive to less than 3 mcg. of streptomycin per cc. of culture medium.

Conclusions. 1. In a controlled study consisting of 85 patients of whom 42 received streptomycin, there was greater improvement in the treated group with respect to increase in body weight, decrease of fever, and sputum weight.

2. Comparison of the roentgenograms showed a decided improvement in the streptomycin treated group.

3. The proportion of sputum conversions was definitely greater in the streptomycin treated group.

4. The greatest advantage in each of the above criteria occurred immediately after the 3-mo. period of streptomycin therapy.

5. Resistance appeared in approximately ½ of the treated patients after 3 mo. of streptomycin therapy. At the

end of 1 year all available cultures in the treated group showed drug resistance.

6. The emergence of resistant strains of organisms in the majority of treated patients strongly emphasizes the necessity for the employment of measures to prevent this development.

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COMPARISON OF THE RESTING ELECTROCARDIOGRAM, EXERCISE ELECTROCARDIOGRAM, AND THE BALLISTOCARDIOGRAM DURING PROLONGED PERIODS OF OBSERVATION

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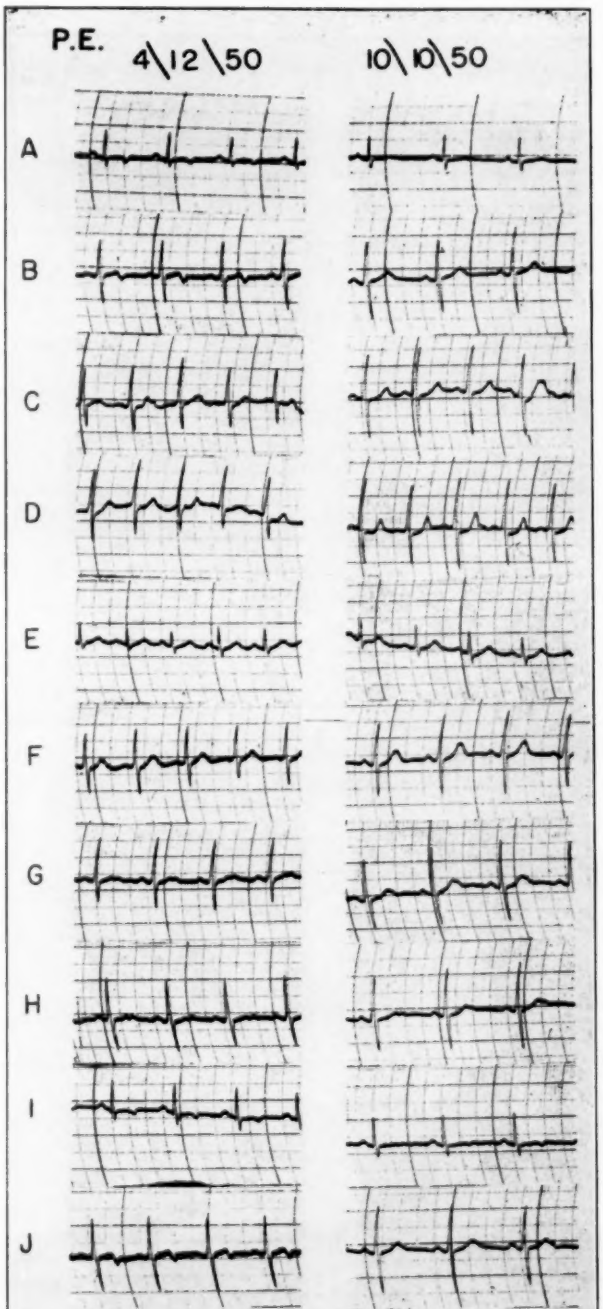
Frequent laboratory and clinical observations were made during an average period of 8½ months upon a group of 11 patients who were experiencing the classical symptomatology of angina pectoris secondary to coronary atherosclerosis. An exhaustive preliminary examination, including gallbladder and cervical spine roentgenograms, was performed in each instance to rule out other possible causes for the subjective complaints. Moreover, it was required that each subject manifest objective evidence of coronary atherosclerosis with abnormal changes in the electrocardiogram in performing the Master 2-step test[3,4].

During the succeeding months these subjects (9 men and 2 women) were taught to live with their disease and they were constantly advised in methods of moderate living. Therapeutic management included specific medicinal agents and definite dietary restrictions[5]. It was expected that the electrocardiogram, both resting and exercise, would show some changes during this prolonged period of investigation and continued observations proved these expectations correct.

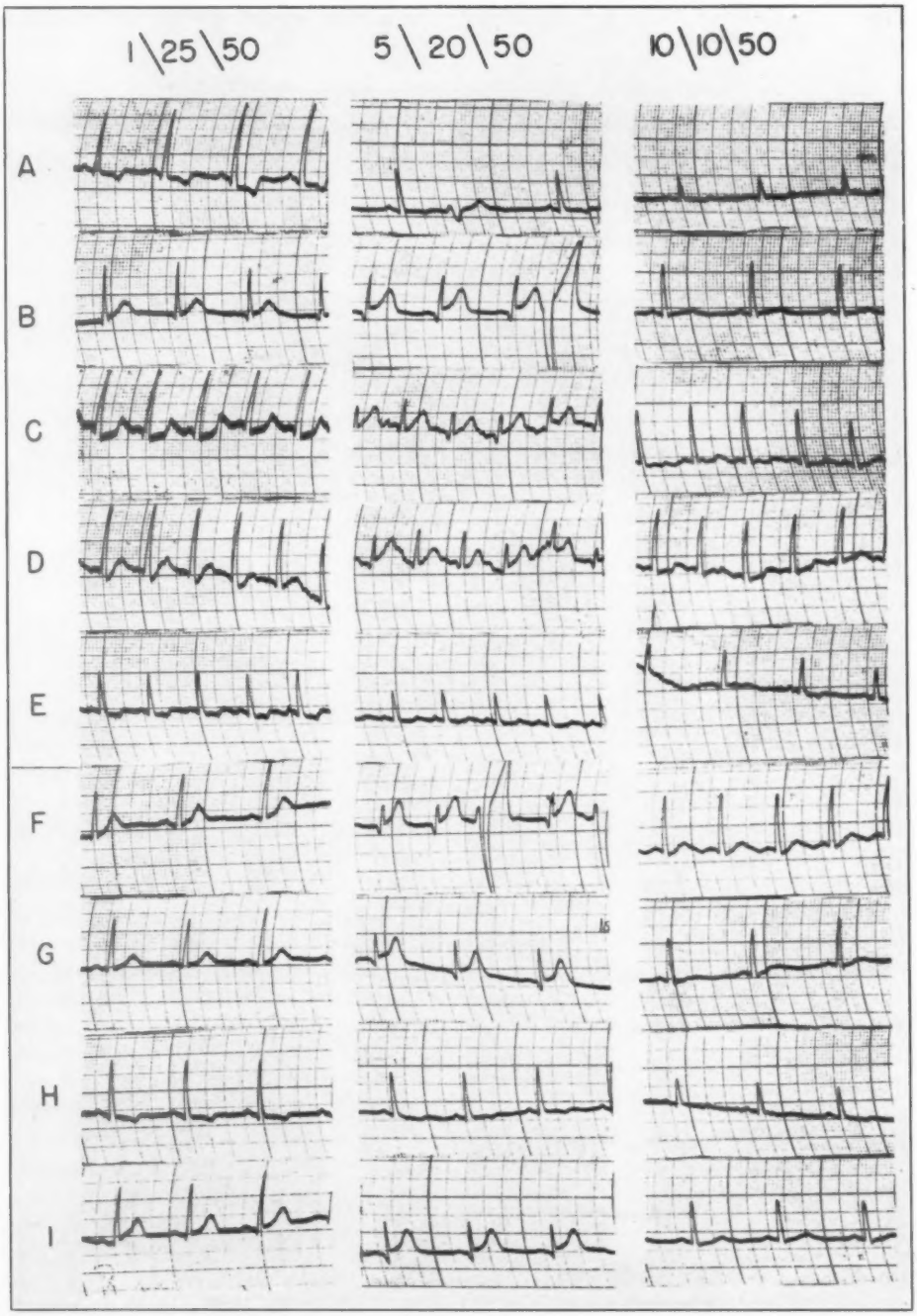
It was decided that it would be most instructive to obtain the ballistocardiographic pattern in these same subjects in a similar period. The questions we wished to answer were: Would the ballistocardiogram be more sensitive than the electrocardiogram in detecting cardiovascular pathology? Would the ballistocardiographic pattern change during prolonged periods of observation, and if so, would it change in the same direction as the electrocardiographic changes during both rest and exercise?

Results. 1. Electrocardiographic and Exercise Tolerance Test Data. In the resting electrocardiograms the T waves in 3 patients showed definite improvement (from an inverted to an upright T wave). Two of these instances are pictured in Fig. 1 and 2. The precordial T wave became worse (from an upright T to an inverted T) in 1 patient (Case 11, W.S., Fig. 3).



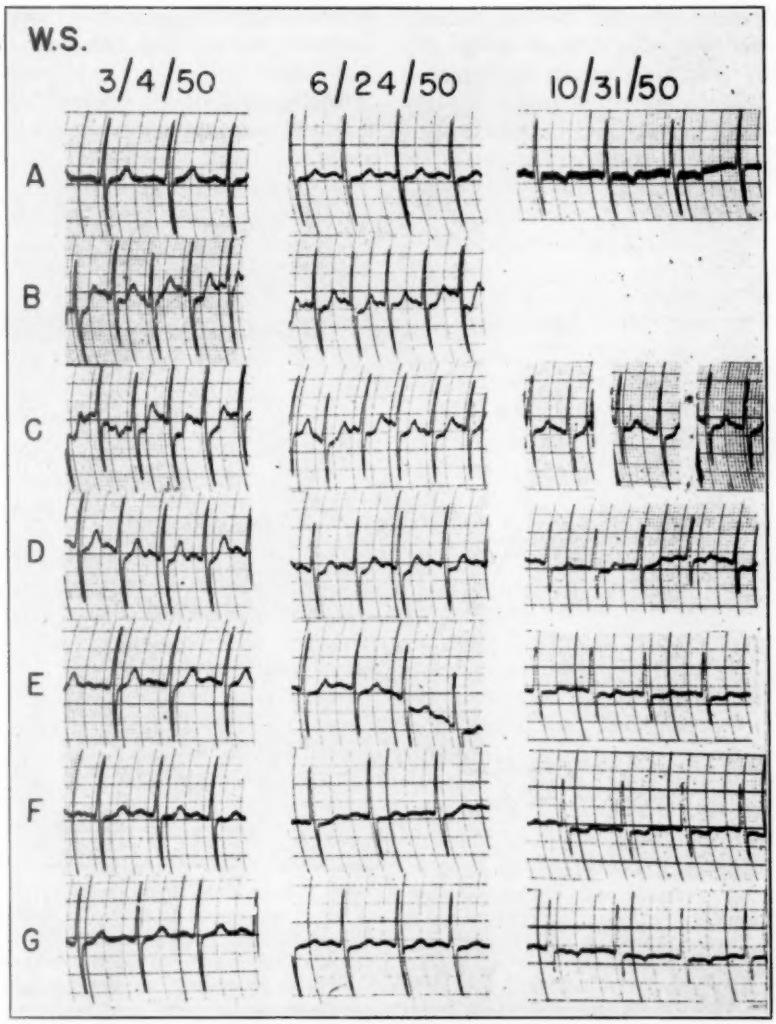
A–Lead I; B–CB_4; Rest.
C, D–Lead CB_4; Exercise.
E, I–Lead I; F, G, H–Lead CB_4; Early recovery.
J–Lead CB_4; Late recovery.

FIG. 1. This 59-year-old male patient (Case 7, P.E.,) experienced the classical symptoms of angina pectoris throughout the period of observation, but there was steady clinical improvement. Both 2-step tests were abnormal (the patient stopped at 2 minutes because of the appearance of mild substernal discomfort). Whereas on 4/12/50 an inverted T wave in Lead I became upright, on 10/10/50 an upright T_1 became inverted during the 3rd minute of early recovery (I). On 4/12/50 the inverted T wave in Lead CB_4 became upright during exercise and early recovery, and on 10/10/50 the upright T wave increased in amplitude during exercise. Significant RS-T depression was present in Lead CB_4 on 10/10/50, but only during exercise.



A—Lead I; B—Lead CB_4; Rest.
C, D—Lead CB_4; Exercise.
E—Lead I; F; G—Lead CB_4; Early recovery.
H—Lead I; I—Lead CB_4; Late recovery.

FIG. 2. Patient 10, T. W., shows consistent improvement in the T waves of the resting electrocardiogram Leads I and CB_4. On 5/20/50 resting T_1 was inverted and became upright immediately after exercise. On 1/25/50 there was significant RS-T depression and on 10/10/50 abnormal T wave changes occurred in Lead CB_4 during exercise only.



A—Rest.
B, C—Exercise first and second minutes.
D, E, F—Early recovery.
G—Late recovery.

FIG. 3. Only Lead CB_4 was taken. Patient 11, W. C., a 43-year old hypertensive woman, evidenced a persistently abnormal exercise electrocardiogram pattern with depressed RS-T segments during exercise and a parodoxical T wave response on 10/31/50. Exercise was stopped at 2 minutes because of substernal pain. Resting T CB_4 showed inversion on 10/31/50.

A total of 28 modified Master double-2-step tests[6,7] was performed on these 11 patients. Lead CB_4 and Lead I were recorded before, during, and after exercise. Lead CB_4, the Wolferth lead, is derived by placing the indifferent electrode under the tip of the right scapula and the chest electrode in the 5th interspace, mid-clavicular line. By using a chest strap to hold these leads in place it is possible to record CB_4 accurately while the patient is walking. The degree of improvement or deterioration of the exercise test after therapy in any given case was determined by the exercise tolerance and by the changes in the electrocardiograms during and after exercise (RS-T segment, T wave, premature beats, and recovery pulse rate).

Of the 11 patients studied 5 showed marked improvement, 2 slight improvement, 1 no change, and 3 definite deterioration in 1 or more items. In regard to the exercise tolerance 4 patients improved, 4 showed no change, and 3 became worse. The RS-T changes were definitely less marked or practically disappeared in 2 pa-

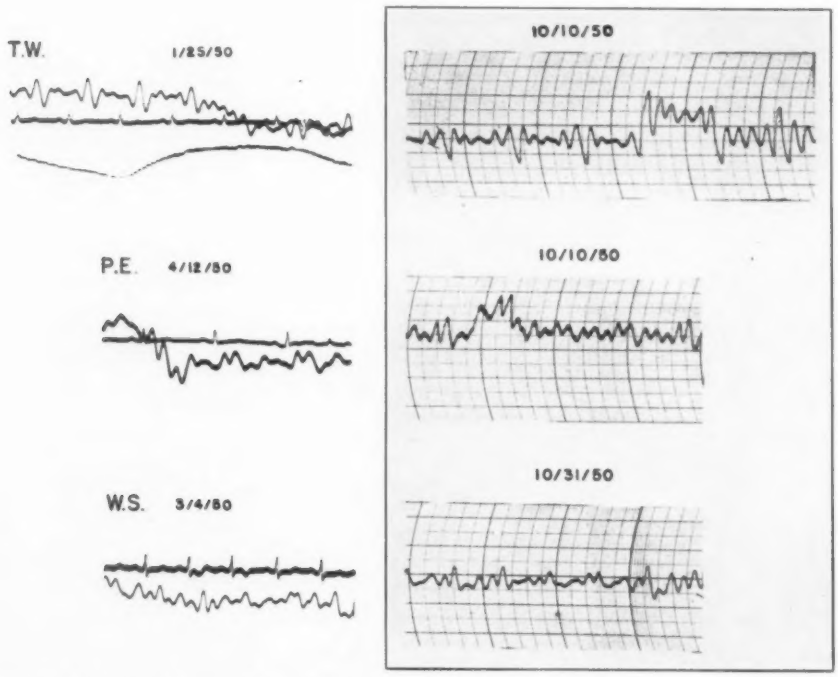


FIG. 4. Ballistocardiograms before and after therapy. Patient T. W. shows minimal deterioration in the ballistocardiographic pattern and patient W. S. evidences no change. Compare with the electrocardiographic changes in Fig. 2 and 3, respectively. Patient P. E. shows ballistocardiographic improvement, that is, higher amplitude on 10/10/50 (note differences in standardization), and this occurred concomitantly with improvement, in his resting electrocardiogram (Fig. 1). Because of severe hypertension a sympathectomy was performed upon patient W. S. in 1947. Her ballistocardiogram shows slurred K waves and these are frequently seen in post-sympathectomy patients.

tients, but in another 2 patients the changes became more conspicuous, the remainder of the patients showing no significant difference. In 1 patient the exercise test before therapy precipitated numerous premature beats, but after completion of the therapy not a single premature beat during or after exercise was observed. In 11 instances (representing 8 different patients) subjective symptoms did not appear even though in each instance diagnostic electrocardiographic evidence of coronary insufficiency precipitated by exertion was recorded. It is interesting to note that in a given subject the improvement or deterioration in the resting electrocardiogram was invariably accompanied by the same trend in the exercise electrocardiogram.

2. BALLISTOCARDIOGRAMS.

The tracings were recorded using a high frequency table and were analyzed essentially as outlined by Brown and associates[1,2]. Of these initial records 9 were considered to be definitely abnormal and 2 were labeled probably abnormal. There was no ballistocardiographic change during or after therapy in 8 of the 11 patients. Case 7, P.E., showed minimal ballistocardiographic improvement. Case 4, F.C., and Case 10, T.W., showed deterioration in their pattern, that is, more irregular complexes.

Discussion. Both subjective and objective (that is, exercise electrocardiograms) findings in these 11 patients gave irrefutable evidence of coronary atherosclerotic disease but in only 4 cases was the resting electrocardiogram abnormal (Cases 5, 6, 7, and 10). In these same individuals, however, the ballistocardiographic pattern was abnormal in 9 cases, and the other 2 tracings were described as probably abnormal. It is apparent, then, that in many instances the ballistocardiogram is a more sensitive tool than the resting electrocardiogram for detecting cardiovascular damage. The abnormal ballistographic interpretation, however, is not as specific as the electrocardiographic interpretation can usually be, for in the former case the observer must occasionally note that "this ballistocardiographic record is suggestive of myocardial disease but pulmonary disease can produce a similar pattern." The comparison of the changes of the electrocardiogram (both resting and exercise) and the ballistocardiogram during prolonged periods of observation presents a much different picture. Ten of the 11 patients studied showed either resting or exercise electrocardiographic changes, but only 3 of these subjects showed ballistocardiographic changes (Table 1). Case number 7, P.E., showed minimal ballistocardiographic improvement; Cases 4, F. C., and 10, T. W., showed deterioration in their pattern, that is, more irregular complexes. Neither the resting nor the exercise electrocardiogram showed significant changes in Case 4, F. C., whereas his ballistocardiogram was interpreted as evidencing a more abnormal pattern following therapy. Seven subjects experienced clinical improvement and the electrocardiographic, ballistocardiographic, and clinical course in 6 of these individuals followed parallel trends. The one exception, Case 10, T. W., showed definite clinical and resting electrocardiographic improvement, but at the end of the period of our observation his ballistocardiographic pattern manifested some deterioration. Clinically no patient became worse.

It is evident that during a similar period of observation the ballistocardiogram showed far fewer changes than did the combined resting and exercise electrocardiogram. As a method of measuring the progress of these subjects objectively the ballistocardio-

gram was, therefore, a less valuable agent than was the electrocardiogram. In defense of the ballistocardiogram, however, the following pertinent observations must be considered. The evaluation of the ballistocardiogram as utilized in our study may well be changed as further observations in clinical ballistocardiography are made, and ballistocardiographic changes which we now consider "minimal" or of "no significance" may then assume a new importance. Secondly, subjects that have been followed a number of years longer than the period of observation described in this study may manifest dramatic changes. For example, the ballistocardiographic tracing of Case 4, F.C., taken on January 30, 1950, showed striking deterioration when compared to a tracing taken on April 24, 1947. Further but minimal deterioration of this pattern occurred during 1950.

Conclusions. 1. Eleven subjects who demonstrated objective and subjective evidence of coronary atherosclerosis were studied for an average period of 8½ months. The resting electrocardiograms, exercise electrocardiograms and ballistocardiograms taken during this period of observation were compared.

TABLE 1.—RESTING ELECTROCARDIOGRAPHIC, EXERCISE ELECTROCARDIOGRAPHIC, AND BALLISTOCARDIOGRAPHIC CHANGES DURING THE PERIOD OF OBSERVATION

Case No.	*Patient*	*Resting Electrocardiogram*	*Exercise Electrocardiogram*	*Walking Tolerance*	*Ballistocardiogram*
1	B. F.		I*		
2	C. L.			I	
3	D. J.		W†	W	
4	F. C.				W
5	L. A.	I		I	
6	M. M.			I	
7	P. E.	I			I
8	P. C.		W	W	
9	R. A.		I	I	
10	T. W.	I			W
11	W. S.	W		W	

* I = Improvement
† W = Worse

2. The ballistocardiogram evidenced abnormalities far more frequently than did the resting electrocardiogram and indeed compared favorably in this respect with the exercise electrocardiogram. As utilized at the present time, however, the ballistocardiogram could not be interpreted as specifically in these instances as could the electrocardiogram.

3. During the same period, the combined resting and exercise electrocar-

diographic tracings showed many more significant changes than did the relatively static ballistocardiographic records. As a method of measuring the progress of these subjects objectively the ballistocardiogram was, therefore, a less valuable agent than was the electrocardiogram.

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THE CLINICAL SIGNIFICANCE OF THE SMALL BENIGN GASTRIC ULCER, WITH A NOTE ON BENIGN ULCER OF THE GREATER CURVATURE AND IN THE ABSENCE OF FREE HYDROCHLORIC ACID

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The subject of gastric ulcer is most often approached in terms of the large lesion and its neoplastic implications. Although this is one of the most important aspects of stomach disease, it must not blind one to the fact that the small benign ulcer may be of tremendous clinical importance in its own right. There is much more to be considered in attacking the problem of gastric ulcer than the differentiation of benignancy from malignancy.

This is a report on a segment of the courses of 100 personally-observed patients with small gastric ulcers. All lesions were benign, and, although during the individual patients' courses differentiation between ulcer and carcinoma frequently proved difficult, benign gastric ulcer is considered here as a specific entity, not as a differential diagnostic problem. "Small" gastric ulcer is defined as a lesion which upon examination, during life or at autopsy, measures no more than 1 cm. in greatest diameter, but which, to eliminate from discussion simple mucosal erosions, is found to be at least a half-centimeter deep.

Material. The 100 patients were studied in the hospital, in most cases for about 4 months, and many were then followed for varying periods as outpatients. Except for one who died of an ulcer complication shortly after the lesion was diagnosed, 54 patients were actively observed for from 4 to 6 months following establishment of the diagnosis, 20 for from 6 to 12 months, and 25 from 1 to 5 years. Following diagnosis, the sum of the observation periods amounted to 87.2 years, or an average of 10.7 months per case.

Fourteen of the patients were women, and 9, one of whom was a woman, were Negroes. The age range extended from 17 to 68 years; the numbers of patients per decade from the second through the seventh were, respectively, 6, 26, 23, 18, 12, and 15. About half of the patients, therefore, were between 21 and 40 years old.

The diagnoses of benign gastric ulcer were in all cases established by the combined use of gastroscopy and roentgenography. In addition, 29 stomachs were resected and became available for study, and 12 others were examined at the time of operative repair of perforation or hiatus hernia. Thus, in only 29 instances was there histopathologic proof of benignancy. The other 71 ulcers were diagnosed as benign at the outset, after concerted consideration by the radiologist, gastroscopist, surgeon, and internist; because they continued to appear benign in all clinical, roentgenologic and gastroscopic manifestations throughout the period of observation, it is believed that the nature of the disease process was substantiated with reasonable assurance for present purposes. Figures indicating the degree of error involved by this means of approaching the differential diagnostic problem have already been presented[11].

Associated Diseases. Pertinent associated diseases were common. Twenty patients also had a duodenal ulcer, and another had peptic ulcers in 4 locations: the esophagus, stomach, duodenal bulb, and descending duodenum. There were 8 instances of hiatus hernia, although in only one was the ulcer located in the herniated portion of the stomach. Gastric polyps were found in 2 patients, and prolapse of the antral mucosa in another. Simple cholelithi-

asis was present in 2, diverticulosis coli in 1, and Saint's triad (these 2 diseases plus hiatus hernia) in another. Two patients had cirrhosis, 1 had Boeck's sarcoidosis, 1 had situs inversus viscerum, and 3 had major psychoses.

ASPECTS OF GROSS PATHOLOGY. In 5 instances there were more than one ulcer. Three patients had 2, and two had 3. All of these lesions were in the antrum.

TABLE 1.—ANATOMIC DISTRIBUTION OF THE LESIONS IN RELATION TO THE TWO MAJOR COMPLICATIONS

	Total No. Cases	*No. Cases Hemorrhage*	*No. Cases Perforation*	*% with Complications*
Pylorus	8	3	1	50
Antrum				
Lesser curve	35	10	3	37
Great curve	6	2	1	50
Anterior wall	7	0	5	71
Posterior wall	14	2	0	14
Pars media				
Lesser curve	17	10	0	60
Great curve	3	1	0	33
Anterior wall	3	0	2	66
Posterior wall	6	1	0	17
Fundus	1	1	0	100

An examination of the anatomic distribution of the ulcers (Table 1) shows that the pylorus was involved in 8 cases, the antrum in 62, pars media in 29, and fundus in 1. In 52 of the patients, the ulcers were on the lesser curvature, in 9 on the greater curvature, in 10 on the anterior wall, and in 20 on the posterior wall (plus 9 in the pylorus or fundus). The breakdown for cases of multiple lesions reveals that both ulcers were on the antral lesser curvature in each of the 3 patients with 2 lesions, and 2 of the 3 ulcers were on the antral lesser curvature in the other 2 patients.

GASTRIC SECRETORY ACTIVITY. The maximum free hydrochloric acid concentration attained upon histamine stimulation (routinely, 1½ hour test, 0.36 mg. of histamine base) was in excess of 70 mEq./L. of free acid in 4 patients. In 20, it ranged between 41 and 70 mEq./L., in 42 between 21 and 40, and in 24 between 6 and 20. Achlorhydria was encountered in 10 patients; in each case no free acid could be elicited by at least 2 histamine-stimulated gastric analyses, plus a 12-hour nocturnal continuous drainage. In one achlorhydric patient there were 2 antral ulcers, and in none of the 5 patients with multiple ulcers could more than 38 mEq./L. of free acid be elicited.

BENIGN ULCER OF THE GREATER CURVATURE, AND IN THE ACHLORHYDRIC STOMACH. In 9 instances the ulcer was located precisely on the greater curvature (Figs. 1 to 3), the curvature for present purposes being defined as the left and the inferior profile lines of the barium-filled stomach, examined roentgenologically in the direct posterior–anterior direction. In 10 patients there was achlorhydria, as previously defined. The greater-curvature localization and achlorhydria were combined in one instance. Regardless of the roentgenologic and gastroscopic impressions, all of these 18 patients were rather automatically considered to

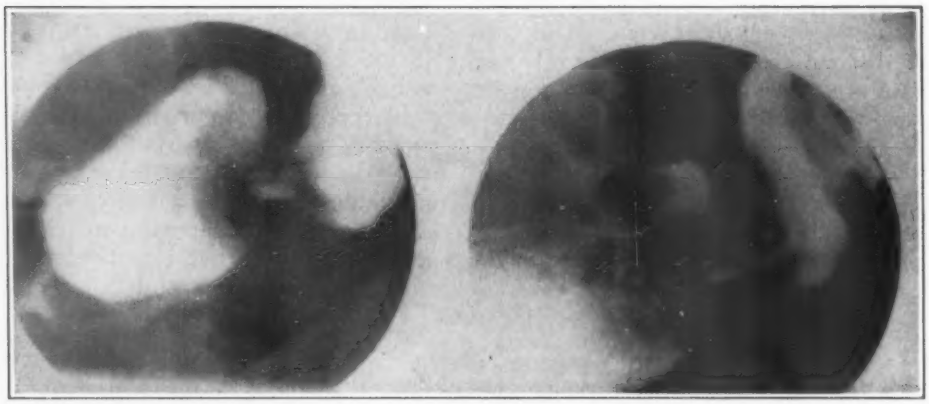

FIG. 1.—Active crater of greater antral curvature in 46-year old man who had complained of typical ulcer symptoms for 4 years. Both the radiologist and gastroscopist considered the ulcer benign, and pathologic examination confirmed the impression.

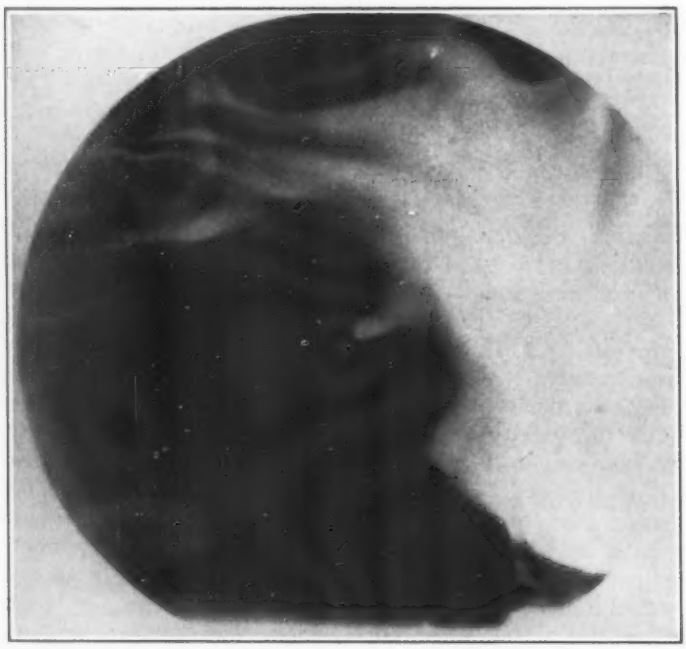

FIG. 2.—This ulcerated lesion of the greater antral curvature was first detected following a sudden hemorrhage. The preoperative diagnosis was benign intramural tumor with ulcer, probably schwannoma. Following resection, however, it was found that the lesion was a simple benign ulcer, with moderate peripheral edema.

have malignant lesions, and all of the stomachs were resected, with pathologic confirmation of the ulcers' localizations and proof of their benignancy. None of the lesions, however, was sectioned entirely from one edge to the other. Six of the greater-curvature ulcers were in the antrum, and the other 3 were in the pars media. The ulcers of 7 of the achlorhydric stomachs involved the antrum and of 3 the pars media.

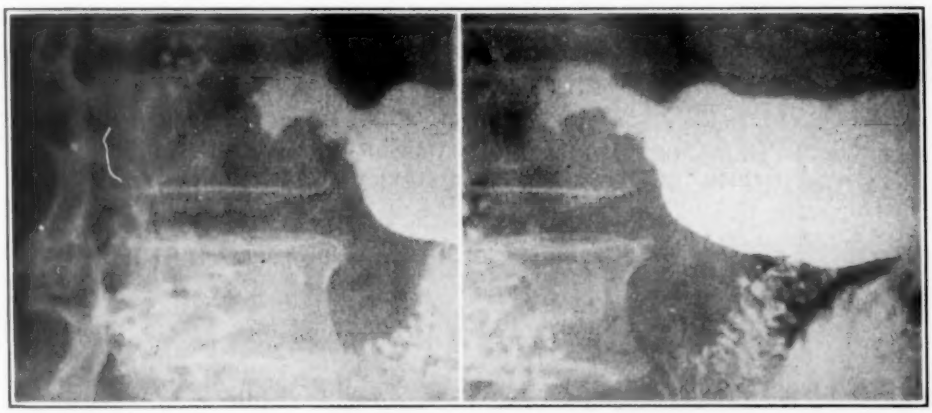

FIG. 3.—This young soldier complained of hunger pains, and the radiologist found a small ulcer of the greater curvature, thought to be within the pyloric canal. Upon gastroscopy, however, it was found to lie just proximal to the pylorus, together with moderate antral gastritis. The pathologist found no evidences of malignancy.

The association of active benign gastric ulcer with true achlorhydria is probably rare. "True achlorhydria" is, however, a difficult diagnosis to make, and, in fact, an acceptably valid definition of the condition can hardly be formulated. In the present series, achlorhydria of the moment was encountered 10 times, as judged by criteria which are probably as rigid as one is able to follow routinely in a clinic or hospital: two 1½-hour gastric analyses with 0.36 mg. of histamine base (adult patients) and a 12-hour continuous nocturnal drainage, at whatever intervals are convenient at the time. In large series of benign gastric ulcers of all sizes, the percentages of patients with achlorhydria have been reported at from 6.7[12] to 19[6]; 10% has been a popular figure[13]. Several detailed cases have been reported[5,10]. It is important to understand, however, that the stomach may temporarily lose its ability to secrete hydrochloric acid, and that the absence of free acid upon repeated gastric analyses does not necessarily prove true achlorhydria[9].

Similarly, the matter of benign gastric ulcer on the greater curvature is difficult to evaluate, largely because of various concepts of the precise location of the greater curvature. If the curvature is defined as a geometric line on the mucosal surface precisely opposite the attachment of the greater omentum, then a particular point of the mucosa may migrate into and out of the line of the greater curvature from time to time, for the mucosa is to some extent mobile over the deeper

gastric layers. Furthermore, the greater curvature would not then correspond exactly to the posterior–anterior profile of the barium-filled stomach. This, plus the fact that to the pathologist the tightly contracted resected stomach often constitutes an anatomic puzzle, makes for some misgivings when one attempts to evaluate certain pathologic descriptions, even those of the greater-curvature purists. Recent reports state that only about 20 valid instances of benign ulcer of the greater curvature have been offered in the literature[1-3,7,8]. There is a commendable note in insistance on carefully documented proof of such a matter, including evidence that the lesion has been sectioned, examined, and found benign microscopically from one edge to the other. But there is danger that distilled statistics emanating from such insistance may be applied to clinical thinking and create a misleading impression of incidences. There is no justification, for instance, for discarding the 6 new cases briefly mentioned by Welch and Allen[13]; this, too, would be invalid. One may reflect on the discrepancy between the oft-stated rarity of the localization in clinical practice, as opposed to an incidence of from 3 to 5% of all benign gastric ulcers found at autopsy[1].

COMPLICATIONS. Forty-five patients had important complications leading to or occurring during the present hospitalization (Table 2), and there were 2 deaths attributable to ulcer. In 30 cases there was significant hemorrhage, defined for present purposes as bleeding of sufficient severity to require replacement by at least 1 liter of blood within the first 8 hours. Sudden hematemesis was the first indication of stomach illness in 6 of the patients. There was no significant sex, race or age predilection for this complication. In 4 instances, active hemorrhage was treated by emergency subtotal gastric resection. One patient died of hemorrhage.

Twelve patients, all males, experienced free perforation, and in 8 this marked the onset of illness. One was treated by emergency subtotal resection and the others by simple closure. One of the latter died 3 days postoperatively.

There were 2 instances of pyloric obstruction, secondary to pyloric ulcer, and both eventually necessitated resection. In one case an ulcer of the antral greater curvature had penetrated superficially into the substance of the liver.

An examination of the incidence of the 2 major complications, hemorrhage and perforation, in relation to the anatomic distribution of the ulcers (Table 1) shows that the patients with posterior-wall lesions had been significantly less prone to serious courses than the others.

It must be emphasized that these major complications occurred in 45% of the patients immediately prior to or during the present hospitalization, not during the entire courses of the

TABLE 2.—NUMBERS OF COMPLICATIONS AMONG THE 100 CASES DURING A PER CAPITA OBSERVATION PERIOD AVERAGING 10.7 MONTHS

	Hemorrhage	*Perforation*	*Obstruction*	*Penetration into Liver*
Total	30	12	2	1
Females	4	0	0	0
Negroes	3	2	0	0

illness. This period was not, of course, a random portion of each patient's course, because frequently it was the complication which led to hospitalization; nevertheless, a distinct tendency for the small lesion to perforate or bleed is evident.

TREATMENT. Medical treatment was exercised in the standard way, with concentration on the usual local and systemic factors. Operation was resorted to 41 times for 41 patients averaging 10.7 months, of 100 patients with benign gastric ulcers which measured no more than 1 cm. in diameter. In 21% there was peptic ulceration elsewhere in the upper gastrointestinal tract, and in 5% there was more than one ulcer per stomach. Achlorhydria, as defined, was present in 10% of the cases. The ulcer was situated on the greater curvature, as defined, in 9%. There were 2 deaths attributable to the lesions, and important complications occurred immediately prior to or during hospitalization in 45%, including severe hemorrhage in 30% and perforation in 12%. Surgical treatment was necessary in 21% for reasons other than suspicion of carcinoma.

TABLE 3.—INDICATIONS FOR SURGERY AND SURGICAL PROCEDURES EMPLOYED

	Indications			
Procedure	*Direct Treatment of the Ulcer*	*"Mistaken" for Carcinoma*	*Perforation*	*Active Hemorrhage*
Subtotal resection	4	20	1	4
Closure of perforation			11	
Repair hiatus hernia	1			

(Table 3). The indications did not in this series happen to include interim treatment for hemorrhage. Sixteen of the operations were done under emergency conditions, either for perforation or active hemorrhage, and 20 stomachs were resected because the lesions were thought to be malignant. Thus, in only 5 instances was surgical treatment resorted to in a considered interim manner for ulcers which did not respond satisfactorily to medical measures; one of these took the form of an indirect attack for a fundal ulcer in a hiatus hernia.

Summary and Conclusions. A study was made of a segment of the courses, averaging 10.7 months, of 100 patients with benign gastric ulcers which measured no more than 1 cm. in diameter. In 21% there was peptic ulceration elsewhere in the upper gastrointestinal tract, and in 5% there was more than one ulcer per stomach. Achlorhydria, as defined, was present in 10% of the cases. The ulcer was situated on the greater curvature, as defined, in 9%. There were 2 deaths attributable to the lesions, and important complications occurred immediately prior to or during hospitalization in 45%, including severe hemorrhage in 30% and perforation in 12%. Surgical treatment was necessary in 21% for reasons other than suspicion of carcinoma.

Small benign gastric ulcers are of particular clinical importance because of their propensities toward serious complications. In proposing therapy for the small ulcer there is much more to be considered than the possibility that it may be malignant. The present study did not, however, include data to suggest that the patient with a small gastric ulcer is necessarily best treated by gastric resection.

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THE FAMILIAL NATURE OF THE AMINO-ACIDURIA OF WILSON'S DISEASE

(HEPATOLENTICULAR DEGENERATION)

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The occurrence of a characteristic amino-aciduria in Wilson's disease, recently described in this Journal[18], provided an important clue to the chemical pathology of this nosologic entity, in which the association of cirrhosis of the liver with specific cerebral degeneration renders the concept of an underlying common metabolic disturbance highly probable. Since then, the presence of persistent amino-aciduria has been confirmed repeatedly by detailed studies on several other patients[2,3,7,8,11,16]. These studies suggest that the amino-aciduria observed in association with hepatolenticular degeneration has certain characteristics that render it peculiar to this disease. These can be briefly summarized thus: (a) The persistent amino-aciduria is independent of the severity of hepatic involvement, being encountered even in those cases in which there is no manifest evidence of liver disease. (b) The amino-aciduria is independent of the amount of total proteins ingested in the daily diet. (c) The amino-aciduria is not accompanied by any significant elevation in the blood alpha-amino-nitrogen level, usually being present even when values for "free" alpha-amino-nitrogen in the blood are normal. Hence, it should be considered distinct in character from the amino-aciduria accompanying severe cirrhosis of the liver or the terminal stages of hepatic failure. (d) There is no specificity in the pattern of amino acids excreted, since all the amino acids normally present in plasma usually are excreted in increased amounts, with daily variations even in individual levels. (e) The severity of amino-aciduria varies in individual cases without any relation to the duration of the disease, insofar as the advent of hepatic failure does not superimpose a secondary amino-aciduria due to failure of deamination of amino acids.

It seems highly probable[11] that the development of cirrhosis of the liver is a result of chronic loss of amino acids, as is seen in the Fanconi syndrome[4-6,9,10], but the actual biochemical lesion that gives rise to the persistent, and often massive, amino-aciduria remains obscure, in spite of the attention focused on this aspect of Wilson's disease. This can be partly ascribed to the fact that most of the recent work has dealt with patients in whom liver disease was manifest in one way or another, thus permitting a diagnosis by clinical symptomatology or by laboratory tests, and rendering studies of peptides and amino acids in

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body fluids of patients of equivocal value because of the superimposition of a second metabolic factor contributed by disturbed liver function. Since the amino-aciduria of Wilson's disease appears to be the cause and not the result of hepatic cirrhosis, attention has been focused[2] on the kidney as a possible site for the abnormally high urinary excretion of amino acids, by invoking the concept of an abnormally low renal threshold for amino acids. However, after intravenous administration of amino acids to patients with Wilson's disease and to a group of normal subjects, no significant differences occurred in plasma levels or in urinary excretion increments[2]. These observations, together with the lack of correlation between the severity of the amino-aciduria and the amount of total protein ingested (and hence the amount of total amino acids available to the blood stream), render the concept of a lowered renal threshold untenable in the light of known patterns of kidney physiology.

As emphasized previously[18], relevant studies can be of unequivocal significance only in cases where there is no evidence of any hepatic involvement, and where the disease is limited to minor neurological disturbances, which, in the presence of Kayser–Fleischer rings, still make a positive diagnosis possible. The probable metabolic defect operative in the pathogenesis of Wilson's disease, in the light of work hitherto accomplished, and the known familial nature of this disorder, made it imperative to establish the presence or absence of amino-aciduria in families where one or more members had succumbed to the disease. The concept of a metabolic disorder leading eventually to development of cirrhosis and probably initiating the degenerative changes in the central nervous system would be tenable only if the amino-aciduria could be shown to be present long before any neurological and hepatic signs or symptoms appeared. This report concerns itself with such a study in a family of which 4 members have died of Wilson's disease. The study is limited to the demonstration of amino-aciduria in the remaining and hitherto unaffected members of the family. An anomaly in peptide excretion accompanying the amino-aciduria is also described. A detailed clinical account of this family will be presented elsewhere[12]. De Verdier's[19,20] chromatographic findings of a generalized increase in urinary amino acids in this family were confirmed.

There follow the clinical data of 12 members of this family.

Case Reports. CASE 1. The mother of the siblings listed was a 45-year old housewife. She had always enjoyed good health. She had no symptoms or signs pointing to neurological or hepatic involvement, and no Kayser-Fleischer rings were present. There were no relevant facts in her past and family history.

CASE 2. The first child was an illegitimate male born in 1923. He has been healthy up to the present time. Examination in May, 1950, yielded no significant physical findings. Results of neurological examination were negative. Kayser–Fleischer rings were not present; laboratory tests, including liver function tests, gave negative results.

CASE 3. The second child, a male born in 1928, died in 1936 of cirrhosis of the liver in Falu Hospital, Sweden. Terminally, marked hepatomegaly was noted. The patient died following an exploratory laparotomy. Biopsy at that time revealed hepatic cirrhosis.

CASE 4. The third child, a male born in 1929, has had no subjective symptoms up to the present time. Examination revealed no significant findings. Results of neurological examination were negative. Kayser–Fleischer rings were not present. Results of laboratory tests, including liver function tests, were negative.

CASE 5. The fourth child, a female born in 1931, died in 1941. She was admitted to the Medical Service of Falu Hospital with tremor in January, 1941. On another admission in October, 1941, a diagnosis of hepatolenticular degeneration was made. The pathological diagnosis was hepatolenticular degeneration.

CASE 6. The fifth child, a male born in 1932, died in 1944. He was admitted to the Medical Service of Falu Hospital in 1942 with the diagnosis of subacute glomerulonephritis. At that time, an episode of albuminuria and glycosuria was observed. He was readmitted in 1944, at which time the clinical picture was identical with that observed previously in the fourth child. A diagnosis of hepatolenticular degeneration was established. The patient died at a local institution for the chronically disabled. Terminally, there was massive tremor of the whole body, and speech was severely disturbed, although intelligence was noted not to be impaired. The patient suffered terminally from bouts of tonic spasms which also affected the pharyngeal muscles, rendering it impossible for him to swallow. These spasms were of short duration and were followed by periods of relaxation. Postmortem examination was not made.

CASE 7. The sixth child, a female born in 1935, died in 1948. She was admitted several times to the Medical Department of Falu Hospital, and during the 1947 and 1948 admissions the diagnosis of hepatolenticular degeneration was established. The neurological symptomatology was of a classical type. Bilateral Kayser–Fleischer rings were present. Exploratory laparotomy revealed cirrhosis of the liver (Laennec's type). Serum citric acid levels of 33 and 41 gamma per 100 cc. were noted. Hanger's cephalin flocculation test was 3 + on repeated tests. Results of other laboratory tests, including liver function tests, were within normal limits. The patient died at home; no postmortem examination was made.

CASE 8. The seventh child was a female born in 1937. She was the first of our patients to show amino-aciduria. She was admitted to Falu Hospital in 1947 and 1948 for study because of the remarkable family history, although she had no subjective symptoms at the time. On her last admission in 1950, a diagnosis of hepatolenticular degeneration was made on the basis of the family history and the presence of massive amino-aciduria. Examination during 1950 showed the beginning of slight hepatomegaly, with the liver edge palpable 1 to 2 cm. below the costal margin. This had not been present from 1948 to 1949. Three spider angiomata were also observed. Throughout the period of observation from 1948 to May, 1950, results of Hanger's cephalin flocculation test were negative. Results of the thymol turbidity test varied between 6 and 7 Maclagan units. Serum citric acid levels of 37, 42, 29, 39, 41, and 31 gamma per 100 cc. were noted by the Thunberg enzymatic method (normal values are less than 27 gamma per 100 cc.). Neurological examination has been completely negative up to the present time. Kayser–Fleischer rings have not been present. An exploratory laparotomy performed in 1948 revealed a normal liver, and a specimen obtained for biopsy during the operation showed normal liver tissue. Another liver punch biopsy performed in February, 1950, after the presence of amino-aciduria was established, showed normal liver parenchyma. (See Table 1 for amino-aciduria.)

CASE 9. The eighth child was a male born in 1939. He has had no subjective symptoms up to the present time. Results of physical examination have been consistently negative. Kayser–Fleischer rings have not been present. Serum citric acid levels of 32, 27, 24, and 36 gamma per 100 cc. have been noted. Results of all other laboratory tests, including liver function tests, have been negative. (See Table 1 for amino-aciduria.)

CASE 10. The ninth child was a female born in 1940. She has had no subjective symptoms up to the present time. Results of physical and neurological examination have been consistently negative. Kayser–Fleischer rings have not been present. Serum citric acid levels of 32 and 43 gamma per 100 cc. have been noted. Results of liver function tests have been negative. (See Table 1 for amino-aciduria.)

CASE 11. The tenth child was a female born in 1942. She has had no subjective symptoms up to the present time. Results of neurological and physical examinations to date have been consistently negative. Results of liver function tests have been negative (Table 2).

CASE 12. The eleventh child was a male born in 1944. He has been healthy up to the present time. Results of neurological and physical examinations have been consistently negative. Serum citric acid levels of 38 and 33 gamma per 100 cc. have been noted. Results of other liver function tests have been negative. (See Table 1 for amino-aciduria.)

STUDIES ON THE URINE. Urine from the subjects studied was collected at Falu Hospital, Sweden, on 3 successive days after each individual had been placed on a protein-poor diet for 1 week prior to the collection. The total

TABLE 1.—DATA ON AMINO-ACIDURIA IN 7 ASYMPTOMATIC SUBJECTS FROM A FAMILY OF 11 CHILDREN, 4 OF WHICH HAD DIED OF WILSON'S DISEASE

	24-Hour urine volume, cc.	*Urinary excretion of amino-N, mg./24 hr.*	*Peptide-N (R_F 0.24–0.48) as % of hydrolyzed total amino-N in urine*
Case 1	1450	110	None
	1500	106	None
	950	80	None
Case 4	1100	110	None
Case 8	700	475	
	1200	1030	32
	1100	430	37
10 months	350	86.2	
later	650	497	28
	1700	990	32
Case 9	1100	220	18
	700	213	14.6
10 months	700	226	
later	800	335	16.8
Case 10	1050	217	17.2
	850	240	22.4
10 months	800	364	11.0
later	1000	384	18.6
Case 11	500	204	16.6
Case 12	500	214	
	850	194	8.0

TABLE 2.—DATA ON HYDROLYZED PEPTIDES IN 4 ASYMPTOMATIC SIBLINGS WITH AMIDO-ACIDURIA IN A FAMILY OF 11 CHILDREN, 4 OF WHICH HAD DIED OF WILSON'S DISEASE

	Hydrolyzed Peptides																*Deaminated peptide hydrolysates*				*2,4-Dinitrophenylpeptide hydrolysates*			
	Serial dilution: Micrograms peptide N/10 microliters																							
	60				*40*				*20*				*10*											
Case	*8*	*9*	*10*	*11*	*8*	*9*	*10*	*11*	*8*	*9*	*10*	*11*	*8*	*9*	*10*	*11*	*8*	*9*	*10*	*11*	*8*	*9*	*10*	*11*
Glutamic acid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	None				DNP-derivatives			
Aspartic acid	+	+	+	+	+	+	+	+	+	+	±	–	+	+	±	–								
Glycine	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	+	+	+	+	+	+	+	+
Cystine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Serine	+	+	–	+	+	–	–	–	+	–	–	–	+	–	–	–	+	+	–	+	+	+	–	+
Threonine	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	–	+	+	+	+	+	+	+	+
Alanine	+	+	+	–	+	–	–	–	–	–	–		–	–	–	–	+	+	+	–	+	+	+	–
Tyrosine	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–
Aminobutyric acid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Leucine (Iso)	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–
Valine	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–
Lysine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Arginine	+	–	+	+	+	–	–	–	–	–	–	–	–	–	–	–	+	–	+	+	+	–	±	±
Histidine	–	–	±	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	+
Methionine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Phenylalanine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Proline	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hydroxyproline	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

volume of each 24-hour urine sample was noted, and 100 cc. aliquots were placed in bottles with thymol crystals as a preservative. The bottles were sealed and shipped by air express to The Children's Hospital, Boston. In our experience, this procedure has proved to be suitable for the handling of urine on which amino acid and peptide determinations are to be made. Aliquots of the urine were then filtered and appropriate aliquots were used: (a) The total amount of alpha-amino nitrogen per cubic centimeter of urine was determined by formol titration as described previously[18]. (b) Smaller aliquots were reduced in volume *in vacuo* for purposes of paper partition chromatography (unhydrolyzed urine). (c) Still other aliquots were hydrolyzed with 6 N (normal) hydrochloric acid in sealed tubes under nitrogen for 18 hours at 110° C. for the study of complete hydrolysis products. None of the urine contained any albumin or reducing substances. Values for total alpha-amino nitrogen obtained from the samples of urine are given in Table 1. The increase in the alpha-amino nitrogen values after hydrolysis of the urine with 6 N hydrochloric acid was between 100 and 200%, and hence the free amino acid-peptide ratio in the urine did not show any significant deviation that could be construed as indicative of peptiduria. Partition chromatography on all samples showed generalized distribution in the amino acids excreted, the proportions varying in the same patient on different days. This confirmed previous observations made on the same subjects[20] as well as those reported by others[2,18].

Peptides became of special interest when urine from the children in Cases 8, 9, 10, and 11 were subjected to serial dilution chromatography. It became evident that all 4 patients were excreting peptides, R_F of which values for phenol water systems lay between 0.24 and 0.48, in much greater amounts than those observed in the studies of urinary peptides of normal and other abnormal subjects. This point was further investigated.

URINARY PEPTIDES. The urine was filtered, reduced to one-fifth volume *in vacuo*, and slightly acidified to pH 5.0. The sediments were centrifuged off and powdered barium chloride was added to the supernatant solutions until these were barely acid to bromthymol blue. The phosphates thus precipitated were removed by filtration. The filtrates were treated with powdered barium hydroxide until they were alkaline to phenolphthalein, and after this, 2 volumes of 95% ethanol were added. The ensuing heavy precipitate was collected, washed once with ethanol, and redissolved in water. The barium was removed by addition of the appropriate amounts of dilute sulfuric acid and removed by centrifugation. The supernatant fluid containing the peptides was now reduced in volume *in vacuo* to one-tenth of its original volume and appropriate aliquots were used for chromatography. Aliquots were analyzed for total nitrogen (micro-Kjeldahl method), and the peptide N was expressed as per cent of total amino-N from the samples of urine which had been completely hydrolyzed. The chromatographic studies showed no free amino acids to be present except the peptides in question. The peptides were eluted off the paper and hydrolyzed with 6 N hydrochloric acid in sealed tubes at 110° for 6 hours, and aliquots of hydrolysates were subjected to serial dilution chromatography. This procedure revealed that although, in addition to the aspartic acid and glutamic acid, the peptide total hydrolysate contained 6 to 8 other amino acids, the dicarboxylic amino acids were 5 to 8 times in excess of the other amino acids

present in the urinary peptides, as evidenced by the disappearance of the other spots on serial dilution while the spots formed by aspartic and glutamic acid persisted (Table 2). It was estimated that the majority (80 to 90%) of peptides excreted in the urine from these patients were peptides of aspartic or glutamic acids, or possibly of both.

This distribution was at variance with the random distribution of excreted peptides found in normal subjects. Therefore, it became important to establish the location of the aspartyl and glutamyl residues in the peptide chain. This was undertaken by 2 different routes. Aliquots of peptide concentrates were placed on measured areas of filter paper and exposed for 2 hours to nitrous acid fumes in small closed chambers. The peptides were then eluted off the paper with water into capillaries containing an equal volume of 12 N hydrochloric acid. The capillaries were then sealed and heated in an oven for 6 hours at 110° C. to effect hydrolysis of the eluted samples. These hydrolysates of deaminated peptides were chromatographed parallel to hydrolysates of previously undeaminated peptide samples. Since deamination by nitrous acid would involve principally the terminal amino group of a peptide, the amino acid at that terminal point would then be expected, after hydrolysis of the peptide, not to react with ninhydrin to give a visible spot. Chromatography of parallel strips showed unequivocally the disappearance of spots formed by aspartic and glutamic acid, while the other amino acids were found to remain in the same concentration. Thus, it seemed to be established that the excess peptide residues excreted in our subjects were aspartyl or glutamyl peptides. It appeared unlikely that both dicarboxylic acids were present in the same peptide chains, since deamination resulted in the disappearance of both from the chromatograms of deaminated peptide hydrolysates. These findings were further confirmed by forming the dinitrophenyl derivatives of the terminal amino acids through the terminal amino group by the use of 2,4-dinitrochlorobenzene as described by Abderhalden[1].* The peptides thus labeled were then subjected to hydrolysis under the same conditions mentioned previously and the dicarboxylic acids were shown to be terminally situated as evidenced by the presence of only the dinitrophenyl derivatives of aspartic and glumatic acids.

Under the conditions employed, dinitrochlorobenzene combines readily with the free amino group of terminal amino acids without causing hydrolysis of the peptide. This was verified by running the dinitrophenyl derivative of the peptides before hydrolysis together with a hydrolyzed sample, and confirming the absence of hydrolytic cleavage during the process employed in the Abderhalden procedure. These chromatograms were developed in systems where the solvents were phenol–water, butanol–glacial acetic acid–water (500:25:50), and benzyl alcohol–butanol–water. The results are summarized in Table 2. Hydrolysis of the DNP-peptides showed only aspartic and glutamic acid derivatives of DNP, while the other amino acids were found in free form, reacting with ninhydrin to give their respective spots.

* The use of 2,4-dinitrofluorobenzene, as extensively employed by Sanger[17], would of course be greatly preferable, as the reaction could then be carried out at room temperature. This procedure is to be recommended for future studies. During this study, dinitrofluorobenzene was not available to the authors, necessitating the use of 2,4-dinitrochlorobenzene in forming the dinitrophenyl derivatives.

Discussion. The present study, while confining itself to the asymptomatic members of a family otherwise heavily stigmatized with hepatolenticular degeneration, serves to illustrate the familial nature of a metabolic defect which has hitherto been observed as an unexplained feature in fully-developed cases of Wilson's disease. That the underlying metabolic disturbance resulting in amino-aciduria in patients with hepatolenticular degeneration may precede the hepatic and lenticular involvement thus becomes more than a matter of conjecture. At the time when the amino-aciduria was first noted, only the patient in Case 8 showed signs of incipient hepatic involvement without neurological symptoms, while those in Cases 9, 10, 11, and 12 were asymptomatic. One cannot help concluding that the hepatic cirrhosis observed in Wilson's disease must be a direct consequence of the chronic loss of amino acids, as has also been suggested by Himsworth[11]. This concept would be in accord with the well-known observation of the high incidence of hepatic cirrhosis by itself in families where one or more members have been found to be affected with hepatolenticular degeneration. The point is also illustrated in this family where the patients in Cases 5, 6, and 7 died as a result of Wilson's disease, while the one in Case 3 was found to be suffering from hepatic cirrhosis at the time of his death. Yet the loss of amino acids *per se*, and the resulting nutritional hepatic degeneration, does not explain the occurrence of degenerative lesions of the nervous system that characterize the disease. It would seem that a second factor, probably related to the metabolic disturbance that is responsible for the amino-aciduria, is operative in evoking the disease entity which is designated as Wilson's disease. Thus, it may be suggested that hepatolenticular degeneration develops as a result of an unknown metabolic disturbance that accompanies a familial chronic amino-aciduria which often, by itself, results in hepatic cirrhosis. Whether the factor responsible for the changes in the nervous system bears any relation to the amino-aciduria which precedes and accompanies the disease remains to be ascertained.

The abnormality in the excretion of peptides in Cases 8, 9, 10, and 11 was discovered quite incidentally in the course of the chromatographic study of the amino-aciduria. It appears probable that de Verdier[19] was faced with the same phenomenon in his study of these subjects, inasmuch as his description of spot No. 34, which disappeared on hydrolysis, seems to correspond to the peptides described here. The increased excretion of dicarboxylic amino acid peptides by our subjects could be considered as a concomitant of generalized amino-aciduria, that is, a manifestation of the decreased reabsorptive capacity of the renal tubules. However, in contrast with the generalized nature of the amino-aciduria, the selective nature of the peptides excreted may be construed as militating against this simple explanation.

The reabsorption of individual amino acids from the glomerular filtrate appears to be dependent on numerous factors, among which are the relative concentration of a particular amino acid in plasma and glomerular filtrate, and the competition offered by the presence and concentration of other amino acids. This has been well described in the review by Neuberger[13]. The concept of a "lowered renal threshold" for any individual amino acid is thus a descriptive term rather than an explanation of a *modus operandi* when increased urinary excretion of a class of chemical substances is con-

sidered in the absence of demonstrable disease of the kidney.

The interference observed in the reabsorption of creatine as a result of competition with glycine, alanine, and glutamic acid[14,15] serves here as an example. It may well be that the excretion of peptides with a terminal dicarboxylic amino acid residue observed in this study constitutes the manifestation of such a competition instituted during the attempt at reabsorption of free amino acids to the exclusion of such peptides. There is, however, a second possibility that appears of greater significance in terms of the whole disease process. If Wilson's disease represents the end-picture of a familial generalized metabolic disturbance engendered by a deficiency of dicarboxylic-carboxypeptidases in tissues, then the excretion, as observed by us, of peptides having terminal dicarboxylic amino acid residues would be expected. Such an eventuality would also lead to a clarification of the unexplained amino-aciduria, inasmuch as the competitive reabsorption of such peptides in preference to, and to the partial exclusion of, free amino acids would result in increased urinary excretion of amino acids in spite of normal plasma amino acid levels. These conditions would satisfactorily explain the lack of correlation between dietary protein intake and urinary excretion of amino acids, as well as the failure to demonstrate in patients having Wilson's disease a lowered renal threshold for amino acids administered intravenously in large amounts[2]. The confirmation of this hypothesis would be attendant on the development of appropriate techniques for the quantitative estimation of different peptidases in the plasma of patients with Wilson's disease and on the study of peptides in the organs of these patients through observations on the hydrolytic cleavage and utilization of appropriate peptide substrates.

The elevated citric acid levels that have been observed in the cases reported here may be construed as reflecting defective handling of dicarboxylic amino acids and their peptides, since the deamination products of these amino acids, oxaloacetic acid and alpha-ketoglutaric acid, both participate in the tricarboxylic acid cycle with the formation of citric acid as an intermediate. Enrichment in citric acid would suggest a reduction in the rate of synthesis of other amino acids through transamination or reductive amination, thus exacerbating the loss of amino acids that is already operative through the amino-aciduria. How the primary metabolic defect, with which we have been concerned, affects the tricarboxylic acid cycle and the role of specific peptidases in shifting the equilibrium in the reversible processes involved in the formation of intermediate products are as yet unknown and must await further study.

Summary. Five of the asymptomatic members of a family of which 4 siblings had died as a result of Wilson's disease were found to have persistent amino-aciduria. The excretion by these subjects of abnormal amounts of peptides with terminal dicarboxylic amino acid residues was also demonstrated. The familial nature of the amino-aciduria and the relationship of the excretion of specific peptides concomitant with this generalized amino-aciduria are discussed.

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HEMOPHILIA: CLINICAL AND LABORATORY OBSERVATIONS RELATIVE TO DIAGNOSIS AND INHERITANCE*

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The recognition that many of the hemorrhagic diseases are caused by a quantitative lack of one of the essential factors required in the coagulation reaction may be regarded as an important advance that has occurred during the past two decades. Progress has been particularly striking in the group of the hypoprothrombinemias because simple but reliable means for determining prothrombin quantitatively have been available since 1935. With the development of the prothrombin consumption test in 1947[9], it has now become possible to estimate, with a fair degree of accuracy, the coagulation defect in hemophilia and in thrombocytopenic purpura. This has not only resulted in a better understanding of these two diseases, but it has also contributed to a relatively simple formulation of the coagulation mechanism.

For the study of a disease such as hemophilia, it is exceedingly helpful to have as a guide a simple practical hypothesis of the coagulation reactions. Though a casual perusal of the current medical literature may convey the impression that the problem of coagulation is becoming more confused, there is actually emerging a fairly general agreement concerning the broad fundamental facts.

It is now accepted by many investigators that at least 5 primary agents are indispensable for the formation of thrombin. They are prothrombin, calcium, labile factor, thromboplastinogen, and a platelet constituent. To be sure, labile factor is also known as factor V, ac-globulin, and thromboplastin co-factor. Thromboplastinogen is probably the same as the antihemophilic globulin of Minot, Taylor[7], and their associates and the prothrombokinin of Lenggenhager[3]. It is certain that circulating blood does not contain preformed thromboplastin. What is generally designated by that term is an activity which results from the composite action of thromboplastinogen and an agent liberated from platelets. It is not known whether thromboplastin is a definite compound formed from the interaction of the platelet and the plasma factors or whether it is merely a mixture of the two. It is experimentally established that neither factor alone can be changed to thromboplastin, that is, become capable of activating prothrombin. Thromboplastinogen by itself, in contact with a foreign surface, does not become converted to active thromboplastin as Lenggenhager[3] and Lozner and Taylor[4] earlier concluded.

Much evidence is accumulating to show that the 5 basic or primary factors interact stoichiometrically to form thrombin. A lack of any one decreases the quantity of thrombin produced,

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and if the reduction is sufficiently marked, defective hemostasis results. In hemophilia, a lack of thromboplastinogen is now fairly convincingly established as the basic coagulation defect. The prothrombin consumption test is the only available method for estimating the thromboplastin activity of blood, and, therefore, it becomes an important means for studying this disease.

Methods: THE PROTHROMBIN CONSUMPTION TEST. The amount of prothrombin remaining after blood has been clotted under standardized conditions is the basis of the prothrombin consumption test. Its validity depends first on the accuracy of determining residual prothrombin in serum and, secondly, on having the proper conditions to clot the blood.

The determination of prothrombin in serum is essentially the same as in plasma except that fibrinogen and labile factor have to be supplied since these are depleted during the clotting of the blood. Fresh oxalated rabbit plasma treated with tricalcium phosphate to remove prothrombin serves as a simple and satisfactory source of both fibrinogen and labile factor. In practice, 0.1 cc. of the serum to be analyzed is added to a mixture of 0.1 cc. deprothrombinized rabbit plasma, 0.1 cc. 0.02 M calcium chloride, and 0.1 cc. rabbit brain extract. The clotting time serves as the measure of the prothrombin concentration in serum. The details of the test have been described[11]. Recent studies[12] have shown that any accelerators or inhibitors that might be formed during coagulation, as has been postulated, are not present in sufficient amounts to influence significantly the serum prothrombin time or to invalidate its reliability as a measure of residual prothrombin.

Significantly, the prothrombin time of serum from platelet-rich native plasma obtained by slow centrifugation (800 r.p.m.) will sometimes be more consistantly low in mild hemophilia than that of the serum from whole blood. While the reason for this occasional difference is not known, it has been found useful in the diagnosis of mild hemophilia to determine the prothrombin consumption of the serums from both plasma and whole blood.

Far more important and difficult than the determination of prothrombin in serum is the problem of attaining the optimum conditions for bringing about the maximum consumption of prothrombin during coagulation. As a guide in devising a standard procedure, one may postulate a scheme as given in Figure 1. This should not be interpreted as a dogmatic theory, but merely as a blueprint of the probable steps that enter into the formation of thrombin. No thrombin can form until platelets disintegrate and liberate the agent, which is designated in the chart as activator. This does not imply that its action is enzymatic but that it apparently is required for the activity of thromboplastinogen. For platelets to disintegrate, thrombin is required, but this agent is so completely and promptly removed by the enormous fibrin surface of the clot[13], that little is left to act on the platelets and, therefore, the consumption of prothrombin is extremely slow and incomplete. Only after clotted blood is centrifuged, which destroys the intimate contact of thrombin with fibrin surface, is the thrombinogenic reaction rapidly brought to completion. Therefore, in determining prothrombin consumption, the time when the clotted blood is centrifuged, is an important detail which, unfortunately, has been neglected in various modifications of the original test.

In practice, 3 samples of 2 cc. of blood are clotted in separate tubes. The first tube is centrifuged 15 minutes after clotting has occurred, the second after 30, and the third after 60 minutes. The prothrombin of the serum is determined in 15 minute intervals. An example of the results obtained on a normal blood and on a platelet-rich plasma are as follows:

	Prothrombin time of serum in seconds Time after formation of solid clot			
Tube	*15 min. Sec.*	*30 min. Sec.*	*45 min. Sec.*	*60 min. Sec.*
Blood I	10½	24	28	27
II		13	23	24
III				14
Plasma	18½	20½	20	20

The problem in human blood is further complicated by the fact that prothrombin activity increases during clotting. The simplest explanation is that part of the prothrombin is in an inactive form. Little is known concerning the activation of the inactive prothrombin (prothrombinogen) except that it requires a rough surface such as glass and that it occurs rapidly during clotting and slowly in stored oxalated plasma. Presumably all of the prothrombin is changed to the active form when the test is carried out according to the technique developed in our laboratory.

When the prothrombin consumption is low, it may be due to a deficiency of thromboplas-

tinogen, as in hemophilia, or to a lack of the platelet factor as occurs in thrombocytopenia. The platelet activator may also be lacking when the platelets are qualitatively deficient. To determine with certainty whether the poor prothrombin utilization is due to a deficiency of thromboplastinogen, it is necessary to determine the prothrombin consumption after adding an excess of an extract of normal platelets. This is a laborious process and is unsuited as a routine test. Fortunately, a simple way was discovered whereby the prothrombin consumption test becomes a more specific method for diagnosing hemophilia. It consists in adding a small amount of heated rabbit brain extract to blood prior to clotting. To avoid confusing the new modification with the standard method for determining prothrombin consumption, the new procedure will be designated as "thromboplastinogen activity test."

THROMBOPLASTINOGEN ACTIVITY TEST. Tissue extracts such as rabbit brain are generally considered to be thromboplastin. This assumption is justified, since the defective consumption of prothrombin in the clotting of hemophilic blood is corrected by the addition of tissue extracts. Interestingly it was found that when rabbit brain extract is heated to 60° C. or higher, it loses its thromboplastic activity, i.e., it no longer corrects faulty prothrombin consumption in hemophilic plasma. Strikingly, such a heated tissue extract retains its potency to cause prothrombin consumption in normal plasma from which platelets have been removed by high centrifugation. Heated rabbit brain extract behaves like a platelet extract. Whether the two are identical requires additional investigation, but this need not deter employing the test for clinical studies. In a study of over 25 cases of hemophilia, the test has given such excellent results, that it appears to be the most satisfacory procedure for diagnosing the disease. The test does not differentiate between mild and severe hemophilia. In nearly all cases, the prothrombin time of the serum from blood, to which heated rabbit brain extract has been added, is 9 to 10½ seconds, irrespective of severity of the bleeding condition.

The details of the procedure are as follows: To a clean test tube (13x100 mm.) containing 4 glass beads are transferred 0.05 cc. of rabbit brain extract which has been incubated at 60° C. for 20 minutes. Two cc. of blood are added, and mixing is effected by inverting the tube once or twice. A paraffined stopper or a paraffin coated tissue (Parafilm) is used to close the tube during mixing. After 15 minutes of incubation at 37° C. the clot is loosened, and after an additional 10 minutes the clotted blood is centrifuged. The prothrombin of the serum is determined, as outlined, 15 and 60 minutes after centrifugation. The range of clotting times of hemophilic blood by this procedure ranges from 8 to 13 seconds. The values for normal blood vary from 15 to as high as 120 seconds. The prothrombin time of the serum from thrombocytopenic bloods is like that of normal blood

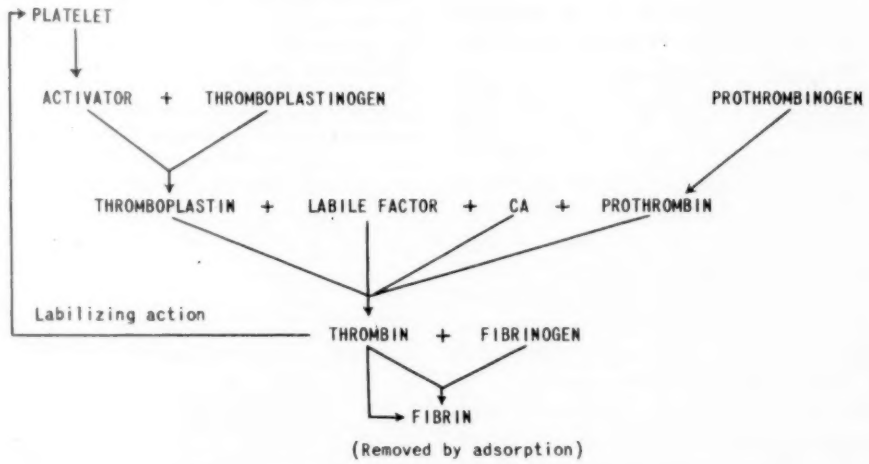

FIG. 1.—A scheme of the coagulation mechanism.

when determined by the new procedure; therefore, hemophilia can be readily differentiated from thrombocytopenia or thrombasthenia.

THE DIAGNOSIS OF HEMOPHILIA. In the past, the diagnosis of hemophilia had to be made almost solely on the triad of a bleeding tendency, a prolonged clotting time, and the characteristic hereditary pattern. None of these 3 findings is, however, specific. On the one hand, a patient with a bleeding tendency due to congenital hypoprothrombinemia may have a history of heredity which may simulate hemophilia; while on the other hand, a patient with a bleeding tendency, a prolonged clotting time, and a normal prothrombin should be tentatively considered to be a hemophiliac even though the family history is negative.

The real difficulty in diagnosis is met with in the individual who consistently has either a normal or only slightly prolonged clotting time, has a negative family history, and has such a mild bleeding tendency that it manifests itself only after operations such as tonsillectomy, tooth extraction, or after severe trauma. Until the prothrombin consumption test was developed, such cases often remained undiagnosed. Even the prothrombin consumption test, carried out by allowing whole blood to clot, may yield equivocal results. By doing the test on the platelet-rich plasma, much more consistent results are obtained (see Table I); but with the new procedure, the thromboplastinogen activity test, an unqualified positive test has been obtained in every one of a series of more than 25 hemophiliacs. By means of the prothrombin consumption test with rabbit brain heated to 60° C., the basic defect in hemophilia can be tested more specifically than by any other known means. Furthermore, the test is simple and rapid. Its application is illustrated by 3 selected cases.

Case Reports. CASE 1. J. K., a white male, age 60, had a spontaneous hematuria which lasted 3 weeks. Although there were many instances in his past history to suggest a bleeding tendency, the true nature of his bleeding was not suspected until the hospital laboratory reported a slightly prolonged clotting time. In fact, a diagnosis of hypernephroma was made on the basis of a pyelogram, and a nephrectomy was considered. On rechecking his history, it was ascertained that he bled during childhood, always had abnormal bleeding after tooth extraction, and frequently developed hematomas after slight trauma. In 1933 he required 3 transfusions to effect hemostasis after a hemorrhoid operation, and in 1946 had to have many transfusions to control hemorrhage after an appendectomy. On physical examination it was found he had partial ankylosis of his left elbow and his left knee. The laboratory findings were as follows: coagulation time (Lee White) 16 minutes; prothrombin time, 12 seconds; bleeding time, 2 minutes; and the tourniquet test, mildly positive. The prothrombin consumption tests were as follows:

	*Sec.**	*Sec.**	*Sec.**	*Sec.**
Blood I	6	12	16	15½
II		9	11	11
III				11
Plasma Thromboplastinogen Activity Time	9	9	10	10
	10	—	—	10

* Fifteen, 30, 45, and 60 minutes after centrifuging.

CASE 2. A male infant born May 14, 1951, bled for 4 days following circumcision. The laboratory findings made at that time (Milwaukee Children's Hospital) were as follows: coagulation time, 10 minutes; prothrombin consumption time,

	*Sec.**	*Sec.**	*Sec.**
Blood I	10	11½	12
II		18½	11½
III			11½

* At 15, 30, and 60 minutes.

The baby was restudied Sept. 4 with the following findings: clotting time (Lee-White) 40 minutes; prothrombin time, 12 seconds; total prothrombin time, 11 seconds; prothrombin consumption time,

	Sec.	*Sec.*	*Sec.*
Blood I	9¼	9	9
II			11
III			12
Thromboplastinogen Activity Time	11	11	11

The baby has been entirely normal, has not bruised nor shown any other sign of a hemor-

rhagic tendency. The family history is negative.

CASE 3. A boy born on December 14, 1941, hemorrhaged following circumcision. The bleeding was controlled locally by pressure. At the age of 1 year, he fell and injured his nose. He had severe epistaxis and since has had many attacks which usually have been controlled by local means, although on several occasions transfusions had to be given. He also bled severely from biting his tongue. When first seen on March 24, 1947, his clotting time was 7 minutes. It was only after observing that his prothrombin consumption test was 11 seconds, that the diagnosis of hemophilia could be considered. He has been repeatedly studied during the past 4 years, and at no time has his clotting time been prolonged. It has remained consistently in the range of 5 to 9 minutes. The family history is negative, except that the mother states that one of her six brothers bleeds abnormally after extraction of teeth. Recent (March 9, 1951) laboratory findings were as follows: clotting time, 9 minutes; prothrombin time, 12 seconds; prothrombin consumption time,

	Sec.	*Sec.*	*Sec.*	*Sec.*
Blood I	10	12	10½	10½
II		11½		10
III				9
Plasma	12	13	12	11
Thromboplastinogen Activity Time	9		9	9

COMMENT. The 3 cases illustrate some of the diagnostic problems of hemophilia. The first patient has only a slightly prolonged clotting time even when the blood is taken with great care in a silicone coated needle and syringe. It is very likely that in the past the clotting time was found normal because it was probably done on capillary blood. That undoubtedly deterred every physician who saw the patient from making a positive diagnosis of hemophilia. As a result the correct diagnosis was not made until the patient was 60 years old. The prothrombin consumption time and the thromboplastinogen activity test are very positive, so that there can be no doubt as to the conclusion that he is a true hemophiliac.

The second patient offers no diagnostic problem. The abnormal bleeding following circumcision, the prolonged clotting time, the typical prothrombin consumption pattern, and the marked deficiency of thromboplastinogen activity firmly establish the diagnosis of hemophilia. Nevertheless, if the child has not been circumcised, the parents would be unaware that he is a bleeder, since he has had no other signs of a hemorrhagic tendency thus far. As pointed out previously, the hemophilic defect is present at birth, but the disease may not be discovered until the baby suffers trauma.

The third patient emphasizes the real difficulty in the diagnosis of hemophilia prior to the development of the prothrombin consumption test. This boy has consistently a normal clotting time, he has only a mild bleeding tendency, and the family history is indefinite. Without the newer tests, a diagnosis of hemophilia could not possibly be made with any degree of assurance. But the positive finding that the thromboplastinogen activity is markedly decreased and the prothrombin consumption is very poor, makes the diagnosis of hemophilia quite certain.

It is to be emphasized that a normal clotting time does not exclude the diagnosis of hemophilia. In a series of 24 cases which one of us reported[10], 7 hemophiliacs had a clotting time of 10 minutes or less. Mersky[6] recently also reported a series of 14 cases of hemophilia with normal clotting times. In most of his patients the hereditary pattern is so definite that there can be no question concerning the diagnosis. The prothrombin consumption test is far more reliable than the clotting time, and the new thromboplastinogen activity test promises to be even more sensitive and specific.

THE CONSTANCY OF THE CLOTTING DEFECT IN THE INDIVIDUAL HEMOPHILIAC. The great variations in the

bleeding tendency in a hemophiliac is commonly regarded as being due to fluctuations in the severity of the disease. This view seems to be supported further by the wide range of clotting times which one finds in examining the records of almost any hemophiliac. A reliable answer to the question whether the clotting defect varies should be obtained by studying patients over a long period with the newer quantitative tests. The writers had the opportunity to study, at frequent intervals, a severe hemophiliac for nearly 6 years.

CASE 4. A white male, age 31, has been a severe bleeder all of his life. He has two older brothers who are likewise hemophiliacs with a bleeding tendency of similar intensity. The family history is otherwise negative. He has had numerous hemarthroses and deep muscular bleeding. He has had 1 attack of hematuria. Epistaxis is infrequent. His bleeding tendency is definitely accentuated during early winter. He has often remained fairly normal for periods of 6 months or longer. His bruising tendency appears to be a fairly good index of the state of his hemostatic dysfunction. During a period of exacerbation, a mere hypodermic injection may cause a large ecchymotic area.

To obtain data concerning the constancy of the clotting defect, the clotting time and later the prothrombin consumption were studied at fairly regular intervals. To conserve space, only the data collected during the first year and during the last 3 months are recorded, since the range of values in the intervening period are essentially the same.

COMMENT. As seen in Table 1, the clotting time varied from 30 to 110 minutes, but the majority of values were in the range of 45 to 60 minutes. It is fairly likely that the clotting times which were less than 45 minutes are attributable to faulty technique. It was repeatedly observed that whenever difficulty was encountered in obtaining the blood, the clotting time was very much shortened and occasionally reduced to as low as 8 minutes. A minute quantity of tissue extract gaining entrance into the specimen is enough to cause such a change. It is very probable that the clotting time is constant, but due to the inevitable slight variations in technique, a range of 45 to 60 minutes is obtained. It is conceivable that slight changes in the blood may occur and temporarily superimpose a further delay of the clotting time. In another hemophilic subject, the clotting time during 3 years remained between 25 and 35 minutes. After transfusions, the clotting time in both subjects became normal, but in a few days returned to the fixed range.

These observations are in accord with the view that the inborn defect in hemophilia is quantitatively con-

TABLE 1.—VARIATION OF CLOTTING TIME AND PROTHROMBIN CONSUMPTION TIME IN A HEMOPHILIAC

Date	*Clotting time** (*min.*)	*Date*	*Clotting time** (*min.*)	*Prothrombin consumption time* (*sec.*)
1945		1946		
Nov.		Aug.		
23	38	15	30	
29	50	22	30	
Dec.		29	45	
Dec.				
6	45	Sept.		
13	40	12	80	
20†	60	19	40	
		21	70	
1946		26	25	
Jan.				
17	80	Oct.		
24	60	30	110	
Feb.		Nov.		
14	50	14	90	
27	50	22	45	
March		1951		
7	75	March		
28	65	7	55	8½
		21	47	8
April				
4	40	April		
11	45	3	65	8½
25	45	10	50	8
		20	85	8
May				
3	70	May		
23	55	8	55	8
29	65	15	70	8
		22	85	8½
June		28	80	8
20	55			
		June		
July		1	80	8
18	40			

* By a standardized Lee-White procedure.
† Bled into left elbow following injury.

stant. The prothrombin consumption test was also found to remain unchanged after the test was rigidly standardized. A value of 8 to 8½ seconds was consistently obtained. The changes in the bleeding tendency are not likely to be due to variations in the basic clotting defect, but rather to changes, such as vascular, that be-

TABLE 2.—SUMMARY OF LABORATORY AND CLINICAL FINDINGS OF HEMOPHILIC FAMILY NO. 1

Subject	Age (yr.)	Clotting time (Lee-White) (min.)	Prothrombin time (sec.)	Thrombo-plastinogen activity time (sec.)		Prothrombin consumption time in seconds				Clinical note
Son J.	5	16	12	9½	Blood I	17	16½	16½	16	Bruises after contusion
					II		17	17	16	Bled from biting tongue
					III				10½	
					Plasma	10½			10½	
Son D.	8	13	12	9½	Blood I	14	13	12½	11½	Bruises easily
					II		9½	15	15	Bled from mouth and tooth extraction
					III				11½	
					Plasma	12½	14		11½	
Son Ti.	9	13	12	10	Blood I	13	12	12	12½	Bruises. Bled from biting lip, tooth extraction and circumcision
					II		11	13	13	
					III				12½	
					Plasma	11½	12½		11½	
Son To.	10	13	12	10	Blood I		13	12½	12	Bruises easily
					II		10	12½	12½	Bled into knee. Bled following tooth extraction and tonsillectomy
					III				12	
					Plasma		11½	13	11½	
Son Ja.	13	11	12	9½	Blood I	13	11½	11½	13	Bruises
					II		12½	12	15	Bled from hematoma and cut in mouth
					III				10	
					Plasma	8	10		10	
Daughter N	16	7	12	16	Blood I	14	28	30	29	No bleeding tendency
					II		15	32	32	
					III				17	
					Plasma	23	25	25	25	
Daughter D	21	9	11½	16	Blood I	11½	19	21	21	No bleeding tendency
					II		12	22	23	
					III				14	
					Plasma	13	19	21	21	
Mother		11	11½	16	Blood I	7	18	19	19	No bleeding tendency
					II		6½	18	19	
					III				13	
Mother's brother	35	10	12		Blood I	7	12	12	12	Mild bleeding until recently. Had serious intestinal hemorrhage
					II		6	14½	13½	
					III				8	
					Plasma	10	10	10	10	

come superimposed on the inherent clotting deficiency.

THE CONSTANCY OF THE CLOTTING DEFECT IN ALL THE AFFECTED MEMBERS OF A HEMOPHILIC FAMILY. Prior to the introduction of specific and standardized laboratory methods for studying hemophilia quantitatively, the only means for estimating the severity of hemophilia were the frequency and intensity of bleeding and the prolongation of the clotting time. Because of vagaries of the hemorrhagic tendency resulting from factors other than the basic defect, and the crudeness of the clotting time, it has not been possible to know whether the various affected brothers of a hemophilic family all have the defect to the same degree or whether there are quantitative variations.

In the present study, 5 families are presented in which 2 or more of the sons are hemophiliacs. In 1 family, the disease is exceedingly mild, in the second family it is also fairly mild, while in the remaining 3 the bleeding tendency is severe. The purpose of the study is to compare the severity of the

hemophilic state in members of the same family as to their clinical and laboratory findings.

Family Reports. FAMILY No. 1. The pertinent data on the members of this family are given in Table 2. Every one of the 5 boys has a mild but unmistakable bleeding tendency. Three of the brothers have bled following tooth extraction, and 2 after circumcision. All bruise markedly after mild contusions. Only 1 had bleeding into a joint which cleared, however, without any ankylosis. The youngest has had only 1 bleeding episode which occurred when he bit his tongue. Two have required hospitalization. The 5 boys lead normal lives, and their play is not restricted. The 2 sisters and the mother are entirely normal. The mother's brother also is a mild hemophiliac who had little difficulty with bleeding, except after teeth extraction, until a year ago when he began bleeding from the intestinal tract. He required 51 transfusions, during the course of several weeks, before the bleeding was controlled.

FAMILY No. 2. Two brothers, aged 31 and 39 years, have had a mild bleeding tendency since childhood. Both bled abnormally following tonsillectomy and have also hemorrhaged after tooth extraction. The older brother bled seriously from lacerations caused by an automobile accident, while the younger had 1 spontaneous episode of gastrointestinal hemorrhage which promptly subsided after 1 transfusion. They have had no other serious

TABLE 3.—HEMOPHILIC FAMILY NO. 2

Subject	*Age (yr.)*	*Clotting time (min.)*	*Prothrombin time (sec.)*		*Prothrombin consumption time in seconds*			
A. M.	39	12	12	Blood I	6	14	13	12½
				II		8	15	15
				III				11
				Plasma	11	11	11	11
L. M.	31	11	12	Blood I	6	14	14	16
				II		8	21	19
				III				13
				Plasma	12½	12½	12½	12½

TABLE 4.—HEMOPHILIC FAMILY NO. 3

Subject	*Age (yr.)*	*Clotting time (min.)*	*Prothrombin time (sec.)*	*Thromboplastinogen activity time (sec.)*		*Prothrombin consumption time in seconds*			
P. F.	11	110	12½	9½	Blood I	11	10	10	10
					II		10	10	10
					III				9½
J. F.	9	135	12½	9½	I	9½	9½	9½	10
					II		9½	9½	9½
					III				10

TABLE 5.—HEMOPHILIC FAMILY NO. 4

Subject	*Age (yr.)*	*Clotting time (min.)*	*Prothrombin time (sec.)*		*Prothrombin consumption time in seconds*			
B. B.	1	7½	12	Blood I	8½	10½	9	8½
				II		10	9	8
				III				9
J. B.	4	30	12	Blood I	9	10½	9	9
				II		10½	10	9
				III				8½

hemorrhages. All their joints are normal. The laboratory data are presented in Table 3.

FAMILY No. 3. Two brothers, aged 9 and 11 years, are severe bleeders. In the older brother, the bleeding tendency was first noticed at the age of 9 months when easy bruising set in. At 15 months he fell and cut his lip. Four transfusions were required to control bleeding. He has had numerous hemarthroses, relatively frequent nosebleeds, and hematuria once. He has a deformed foot due to an old hemorrhage. The younger brother has a similar history, except that he has had only one nosebleed, no hematuria, and less crippling deformities of joints. At the time of study, he had a deep hematoma in his left calf. The laboratory findings are summarized in Table 4.

FAMILY No. 4. Two brothers, aged 1 and 4 years, are both bleeders. The older brother bled after circumcision. He has had numerous bleeding episodes. He bled from biting his lip and has had several large hematomas, 1 of which involved the ankle and dorsum of his left foot. He has had several transfusions. The younger brother also bruises easily after mild contusions, but thus far he has had few serious bleeding episodes. He has required only 1 transfusion. The laboratory findings are given in Table 5.

FAMILY No. 5. Three brothers, J., 13 years, E., 11 years, and L., 7 years, are severe bleeders. J. bled severely after circumcision. He bruises easily, hemorrhaged after tooth extraction, and has had hemarthroses of his knees and ankles. E. also bruises easily, has had even more joint involvement than J., and bled severely after a tooth extraction. Both have required 6 or more hospitalizations and several transfusions. The youngest also has had serious episodes of bleeding, but so far he has had less trouble than his 2 brothers. His left elbow, however, is deformed. He bruises easily, and he has required transfusions to control bleeding. The family history is negative except that the mother's father had nose bleeds during his youth. One brother and 3 sisters are free of any bleeding tendency.

Comment: In comparing the findings of the 5 families, one is impressed with the fact that all the affected members of any one family are very similar both clinically and in regard to the clotting factors in their blood. Thus, the 5 boys of the first family have a mild bleeding tendency. They have had few hemorrhages, have had no crippling hemarthroses, and only 2 of the boys have required hospital care. In contrast, the 2 brothers of the third family and the 3 brothers of the fifth family have many joints ankylosed due to hemorrhage. All have required transfusions to control bleeding. Particularly interesting are the 2 brothers of the second family. Their bleeding tendency is so mild that during the first 30 years of their lives neither has had more than 3 or 4 bleeding episodes. They are gainfully employed, lead normal lives, and rarely are troubled with hemorrhage; in fact, one has not even had minor bleeding during the past 5 years. The 2 boys of the fourth family are severe bleeders. All have required hospitalization and transfusions. More serious hemorrhages will, undoubtedly, occur as they grow older.

To grade hemophiliacs accurately in regard to the severity of the bleeding condition on the basis of the clinical history is beset with difficulties, since external factors such as trauma often determine the frequency of bleeding episodes. Nevertheless, the differences in the bleeding in various hemophiliacs is so marked that one can classify them as severe, moderate, mild, and perhaps even as subclinical. In the first group, hemarthroses are common, while in the mild cases they are usually absent. Mersky[6] and Dunn and Lyons[2] have emphasized that joint bleeding occurs in the severe type of hemophilia but rarely in the mild cases. In none of the families studied, has it been observed that a mother had both mild and severe hemophilic sons.

To determine entirely objectively whether hemophiliacs vary in regard to a specific lack of a clotting factor, a quantitative estimation of thromboplastin activity by means of the prothrombin consumption test seems the most satisfactory approach.

The value of the test to show the marked similarity of the clotting defect in the hemophilic subjects of the same family is clearly illustrated by the results in Table 6. The prothrombin consumption time is practically the same for each of the 3 boys; and, significantly, when the mother's plasma was mixed with an equal volume of each of the boys' plasmas, the correction of the hemophilic defect, as measured by the test, was almost identical in each case.

TABLE 6.—HEMOPHILIC FAMILY NO. 5

Subject	*Age (yr.)*	*Clotting time (min.)*	*Prothrombin time (sec.)*		*Prothrombin consumption time in seconds*			
L. G.	7	70	12	Blood I	9	9	9	8½
				II		9	9	8½
				III				8½
				Plasma	8½	8½	8½	8½
				Plasma of mother 1 cc.				
				Plasma of L. G. 1 cc.	28	28	28	27
E. G.	11	95	12	Blood I	9	9	8½	8½
				II		9	8½	8½
				III				9
				Plasma	9	8½	8½	8½
				Plasma of mother 1 cc.				
				Plasma of E. G. 1 cc.	25	25	25	24½
J. G.	13	80	12	Blood I	10½	9½	9	8½
				II		9½	9½	9½
				III				9½
				Plasma	9½	9½	8½	8½
				Plasma of mother 1 cc.				
				Plasma of J. G. 1 cc.	28	28	28	27½

Discussion. Until the prothrombin consumption test became available, the diagnosis of mild hemophilia was in many instances not possible. Even now, many hemophiliacs whose bleeding tendency is mild and who have a normal clotting time and a negative family history, remain undiagnosed. Occasionally, the prothrombin consumption determined on serum obtained from clotted whole blood may show equivocal results as Mersky[6] has likewise noted. If the test is carried out on platelet-rich plasma instead of whole blood clots.

In mild hemophilia the prothrombin consumption time may be erratic if determined on the serum obtained from clotted whole blood. This is clearly illustrated in Table 2. The prothrombin consumption time of both D. and J. is within the low normal range. The prothrombin concentration of the serum obtained from platelet-rich plasma is definitely in the hemophilic range and is very similar in each of the 5 boys. Most consistent, however, is the thromboplastinogen activity, which is 9½ to 10 seconds in each of the 5 boys; but this helps little in determining the severity of the condition, since similar values are obtained in patients with a pronounced bleeding tendency. No satisfactory explanation can be offered for the apparent high consumption of prothrombin in very mild hemophilia when whole blood clots.

whole blood, the results are more definite and specific. Fortunately, the new thromboplastinogen activity test, in which blood is clotted after the addition of rabbit brain extract heated to 60° C., yields results which even in the very mild cases is strongly positive. With this procedure, hemophilic blood yields a serum which has a prothrombin time of 8 to 12 seconds, while that of normal blood is 16 seconds or higher.

It is important to emphasize that a normal clotting time does not exclude a diagnosis of hemophilia any more than it does a diagnosis of hypoprothrombinemia. In mild hemophilia it is probable that the thromboplastinogen may be reduced sufficiently to cause defective hemostasis but not enough to prolong the clotting time. This is in principle what has been known of hypoprothrombinemia since the prothrombin test became available. The quantitative determination of thromboplastinogen by the tests described offer the most reliable means known, not only for diagnosing hemophilia but also for estimating the severity of the disease.

One of the important unanswered questions concerning hemophilia has been whether the defect varies in intensity or remains constant. Studies on a small number of hemophiliacs over a period of several years suggest that the specific coagulation defect does not alter significantly throughout life. Babies on whom the diagnosis of hemophilia were made soon after birth by means of the prothrombin consumption test have remained bleeders, and there has been no indication that the deficiency of thromboplastinogen changed with age. A small number of sons of known carriers who were found normal at birth have remained free of any bleeding tendency and have maintained a normal prothrombin consumption. It seems justifiable to conclude that the clotting defect responsible for hemophilia is present at birth and remains quantitatively unchanged. With the standardized prothrombin consumption test, it will be possible to test more conclusively the validity of this conclusion.

Certain suggestive collateral information can be obtained from congenital hypoprothrombinemia. In the 5 cases we have studied over periods ranging from 4 to 8 years, the prothrombin time has remained fixed. Occasionally the prothrombin decreases a little, but on administering vitamin K it is restored to its original level, but not above it. With plasma transfusions, the prothrombin concentration can be greatly increased, but within a few days the characteristically fixed prothrombin time is again obtained. Two brothers who have a prothrombin time of 19-20 seconds have a mild bleeding tendency which is clinically indistinguishable from hemophilia. Although the prothrombin level remains constant, they tend to have phases of accentuated bleeding while at other times they have hemorrhages only after gross trauma such as tooth extraction or deep cuts.

One can postulate that in a congenital condition such as hemophilia or hypoprothrombinemia the defect is quantitatively constant. The bleeding tendency, however, may vary because either an additional clotting disturbance may be superimposed on the basic deficiency, or a vascular dysfunction may develop, which, in the presence of the clotting defect, greatly accentuates the bleeding tendency. Mersky[6] has recently also stated that the degree of the defect seems to remain constant over long periods of time. It is to be emphasized that a child cannot "outgrow" a disease such as hemophilia and congenital hypo-

prothrombinemia, nor do they develop it after birth.

During the past 10 years, we have repeatedly observed that if there were several hemophilic brothers they had a similar clinical history and approximately the same clotting time. When the prothrombin consumption time test was developed, it became possible to determine more precisely whether the coagulation defect is quantitatively the same in all members of a family. From the data presented in this paper, it seems fairly certain that it is. Mersky[6] has arrived at a similar conclusion. He states, "The degree of the defect was constant in any family even over a number of generations." This is probably too broad a generalization, especially since the type of the modification of the prothrombin consumption test[5] he employed is subject to technical errors.

There is evidence that a carrier not only transmits the clotting defect but also the degree of the defect. All the affected sons, therefore, have the same amount of thromboplastinogen deficiency, and the carrier daughters apparently transmit the defect in the same quantitative manner. The latter conclusion is still hypothetical, since too few studies have been made.

Congenital hypoprothrombinemia furnishes interesting information in regard to the transmission of a specific clotting defect. In 1 type, the low prothrombin level is definitely inherited[8]. In 1 family which we have studied extensively, the mother has a prothrombin time of 15½ to 16 seconds. One son and 1 daughter have the same prothrombin time as she has, whereas the father and 2 sons have a prothrombin time of 12 seconds, which is normal. Clearly, in this family the defect is quantitatively transmitted by the mother. Unfortunately, there has been no opportunity to find whether the male also transmits the defect quantitatively.

It becomes of practical importance to learn whether the clotting defect in hemophilia can be altered. While there is some evidence that the defect can pass through several generations of females unchanged, it is still undetermined whether the hemophiliac transmits his defect quantitatively to his offspring. Furthermore, the question arises whether the normal parent has any influence on modifying the intensity of the defect.

In regard to the latter problem, the careful studies of Bogart and Muhrer[1] on the hemophilic-like disease of swine may perhaps have some bearing. The latter disease occurs in both sexes and is transmitted by the male as well as the female. All offspring are bleeders if both the boar and the sow are bleeders, but all are nonbleeders if 1 of the parents is normal. On mating 2 carriers, some of the offspring will be active bleeders.

While one cannot reason by analogy in regard to this problem, one must not exclude the possibility that the apparently normal parent may perhaps in some instances modify the hemophilic defect. Since hemophilia may be so mild that it is diagnosed with difficulty, one can conclude that it may even be subclinical, just as there is subclinical hypoprothrombinemia. It is interesting to speculate whether the defect would be accentuated if the father had subclinical hemophilia and the mother were a carrier. With the availability of a quantitative method for determining thromboplastinogen, many of the problems of heredity can be studied more accurately.

Summary. The diagnosis of hemophilia on the triad of a bleeding tendency, prolonged coagulation time, and a positive family history often

fails. A hereditary history frequently is not obtainable, and in mild hemophilia the clotting time may be within the normal range. The prothrombin consumption test is consistently positive except in very mild cases. By carrying out the test on serum obtained from the clotting of platelet-rich plasma instead of whole blood, a positive test is obtained even on very mild cases. By means of a new procedure named "thromboplastinogen activity test," which consists in adding heated rabbit brain extract to blood and determining the prothrombin of the resulting serum, a low consumption of prothrombin is found in even extremely mild cases of hemophilia.

The hemophilic defect appears to remain unchanged throughout the life of the individual. The changes in the bleeding tendency are probably induced by secondary factors superimposed on the basic deficiency. The transmission of the hemophilic defect appears to be quantitative, that is, all the affected sons of a carrier are alike both clinically and in the clotting defect, as determined by specific tests such as the prothrombin consumption time.

One private patient of Dr. Steve Chojnacki and one of Dr. Ely Epstein are included in the reported cases. The writers express their gratitude to them for this cooperation.

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METASTATIC CARCINOMA OF THE SPLEEN

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Metastatic carcinoma of the spleen is considered to be a rare lesion[3,10], and has even been considered sufficiently uncommon to merit single case reports[2]. There is a paucity of recent large autopsy series on this subject, although there have been several excellent reviews published[4,7,11].

There is considerable question as to whether or not the human spleen produces inhibition of tumor growth lodged within it. Experimental evidence, although frequently conflicting, suggests that splenic tissue and its extracts may inhibit tumor metastases[8, 12,13]. Histologic evidence of such inhibition was described by Krumbhaar[7] in the form of fibrosis around metastatic nodules. On the other hand, Herbut and Gabriel[6] deny that the fibrous tissue proliferation in metastatic tumors of the spleen is in excess of that intrinsic to the tumor itself. Further study of this phenomenon would seem to be fundamental in determining tissue susceptibility to cancer.

Method and Materials. Protocols from 19,700 consecutive autopsies performed at the Los Angeles General Hospital were used as the basis of this study. In this group, 2833 carcinomas were encountered, 108 of which were reported to have metastasized to the spleen. Forty-one were rejected as splenic metastases because of lack of histologic proof or absence of tumor in the splenic pulp, leaving a group of 66 histologically confirmed cases of metastatic carcinoma of the spleen.

We have used Warren and Davis'[11] definition of splenic metastases as a "noncontiguous secondary nodule of tumor cells." We have excluded those cases in which the tumor involved only the splenic capsule, since such spread represents peritoneal and not organ metastasis. Since the white and red pulp of the spleen do not contain lymphatic channels, tumor limited to these sites must be considered evidence of hematogenous spread.

Results. There were 66 verified splenic metastases in 2833 carcinomas encountered in 19,700 autopsies. The incidence of metastatic splenic involvement was 0.33% of the total autopsies performed and 2.3% of the carcinomas.

The metastatic epithelial tumors encountered in the spleen most frequently originated in the lung (bronchus), breast, skin (malignant melanoma), and cervix. The order of frequency of organ involvement given by different authors is compared with our own Table 1. Krumbhaar[7] in a series of 6500 autopsies did not find a single case of metastatic carcinoma of the spleen due to bronchogenic carcinoma, which was the commonest primary site in our series.

Histologic Studies. Microscopic sections of the spleen stained with hematoxylin and eosin were available for study in 55 of the 66 cases. These tumors were carefully studied for evidence of inhibition of tumor growth as evidenced by necrosis, fibrosis, or other degenerative changes in the tumor. There was necrosis in 14 of the splenic metastases. This change was

TABLE 1.—FREQUENCY OF SPLENIC METASTASES

	Warren and Davis[11]			Herbut and Gabriel[8]			Abrams, Spiro and Goldstein[7]			Hirst and Bullock*		
Number of Carcinomas Reported	1140			640			1000			2833		
Number with Splenic Metastasis	46			23			90			66		
Primary Sites	*No. Cases*	*No. with Spl. Inv.*	*% with Spl. Inv.*	*No. Cases*	*No. with Spl. Inv.*	*% with Spl. Inv.*	*No. Cases*	*No. with Spl. Inv.*	*% with Spl. Inv.*	*No. Cases*	*No. with Spl. Inv.*	*% with Spl. Inv.*
Lung (Bronchus)	13	3	23	66	4	6	160	15	9.4	397	15	3.7
Breast	193	28	15	26	3	11.5	167	28	16.8	186	13	6.9
Melanoma				8	1	12.5				32	7	21.8
Cervix	162	2	1							226	6	2.6
Ovary	35	2	6	17	1	5.8	64	17	27	79	4	5.0
Other Site or Undetermined	640	8	1							45	5	11.1
Pancreas				31	4	12.9	32	0	0	175	3	1.7
Colon & Rectum	115	3	3	34	1	2.9	205	11	5.3	355	3	.8
Liver										48	2	4.4
Pharynx										32	2	6.2
Testicle										14	2	14.2
Gallbladder										83	2	2.4
Kidney							34	2	6	70	1	1.4
Bladder				28	2	7.1				135	1	.7
Maxillary antrum				1	1	100						
Stomach				76	4	5.3	119	7	5.8			

* Present series

invariably central rather than peripheral, suggesting that the tumor had outgrown its blood supply rather than any anti-neoplastic property of splenic tissue. In 10 of the 14 cases with necrosis, similar changes were seen in other organs involved by the same tumor. In the 4 cases in which only the splenic metastases showed necrosis, the lesions resembled infarcted tumor, suggesting a fortuitous occurrence rather than any local immunity of the tissue to carcinomatous metastases.

Twenty-four of the metastatic tumors of the spleen showed some degree of fibrosis. In 20, however, a similar desmoplastic process was encountered in other organs involved by the neoplasm. In 4 cases a peripheral pseudocapsule was noted in the absence of a desmoplastic tumor. Such capsules incompletely encircled the tumor and were obviously formed by the trabeculae of the organ.

In 40 cases in which slides of the primary and metastatic lesions were available for comparison, there were no detectable differences between the cytologic details of the metastases in other organs as compared to those in the spleen, with reference to staining reaction, nuclear size, nuclear-cytoplasmic ratio, or number of mitoses. Again, no inhibiting effect of splenic tissue on tumor metastases was observed.

Discussion. The frequency of splenic metastases in persons with carcinoma usually ranges from 0.3% to 9% in various reported autopsy series[1,4,7,11] Yokohata[14], studying serial sections of the spleen, was able to demonstrate microscopic metastases in 34% of patients dying of carcinoma. Harman and Dacorso[5] have recently questioned the significance of such studies, arguing that a requisite for the assessment of the resistance of an organ to metastatic involvement is that it be adequately exposed to metastases. Limiting their study to 30 patients with carcinoma who had secondary growths in one or more viscera in both thorax and abdomen, they found a 50% incidence of splenic involvement. They found that whereas lymph nodes, lungs, and liver were the most frequent sites of metastases, the spleen came next and led the pancreas and bone marrow in likelihood of metastatic involvement. They did not publish observations relative to the histologic effect of the spleen on the tumors in their study.

Further evidence that the frequency of metastatic tumors is determined by the mechanics of circulation and not by any peculiar property of the organs themselves has been found by McCutcheon *et al.*[9]. These observers injected cell suspensions of Brown-Pearce tumor into the left ventricle of rabbits and sacrificed half the animals immediately. The other animals were allowed to survive long enough for tumors to develop. The results in these 2 groups indicated that the metastatic tumors were numerically proportional to the tumor emboli that reached the various organs. There is thus a growing body of evidence favoring the mechanistic theory rather than the theory of an inherent antipathy of the spleen to metastatic tumor (that is, "soil hypothesis").

Summary. 1.) In 19,700 consecutive autopsies, 2833 carcinomas were encountered. There were 66 histologically proved metastases to the spleen, an incidence of 2.3%.

2. Metastatic carcinoma in the spleen was secondary to a primary source in the following order of frequency: lung (bronchus), breast, skin (malignant melanoma) and cervix.

3. No inhibiting effect of splenic tissue on carcinomatous growth was observed by histologic studies. This finding favors the mechanistic theory of splenic metastasis.

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PENICILLIN AND CHLORAMPHENICOL IN THE TREATMENT OF INFECTIONS DUE TO PROTEUS ORGANISMS

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The relative resistance of *Proteus* organisms to most of the antibiotics appears to have caused an increased number of infections due to this species[2,9,12,14,15]. Neomycin, chloramphenicol, and gantrisin are the three agents most effective against infections due to Proteus organisms[1,7,11,14,15]. However, the toxicity of neomycin appears to contraindicate its general use and neither chloramphenicol nor gantrisin is always effective in eradicating *Proteus* infections[7,15]. Preliminary *in vitro* studies of numerous strains of *Proteus* organisms revealed that many were extremely sensitive to penicillin, and statistically significant additive as well as synergistic effects were observed when penicillin and chloramphenicol were combined[12]. Thus it appeared of value to determine whether or not these *in vitro* findings had any clinical application. In the following report the results of treatment in 23 cases of infections due to *Proteus* organisms are presented together with the *in vitro* sensitivities of the causative strains to penicillin, chloramphenicol, and the combination of both antibiotics.

Material and Methods. With the exception of one case (Case 1) which has been reported in detail elsewhere, all the cases represented urinary tract infections and were treated on the wards of the Minneapolis General Hospital[12]. The diagnosis was established in each case by at least 1 and usually several urine cultures that yielded only Proteus bacilli. The organisms were identified by the bacteriology laboratory of the Minneapolis General Hospital. The criterion for clinical response was sterilization of the urine as determined by at least 1 sterile culture. Whenever possible, the following therapeutic regimen was followed: 300,000 units of crystalline penicillin G given intramuscularly twice a day for 3 days; following this chloramphenicol was administered in a dose of 0.75 gm. 4 times a day for 3 days. Then if Proteus organisms still appeared in the urine, the 2 drugs were given simultaneously in the same dosage for a similar period of time. Therapy was stopped as soon as sterile cultures were obtained. The initial cultures were tested for sensitivity to penicillin and chloramphenicol• by the tube-dilution method of Rammelkamp and Maxon[8] as modified in this laboratory[13]. This method determines the bacteriostatic activity of the drug tested.

Results. A. In vitro Tests. In 20 of the 23 cases, *in vitro* sensitivity tests were performed with the organisms isolated from the patients prior to therapy (Table 1). Three of the strains were relatively resistant to chloramphenicol (that is, they grew in 100 mcg./cc. of the drug); 6 stains were relatively resistant to penicillin; and only 1 of the 20 strains was resistant to the combination of penicillin and chloramphenicol (Table 1). In 12 instances the combination of chloram-

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• The chloramphenicol used in this study was provided by Dr. R. J. Buckman Director of the Department of Therapeutic Development of the Parke, Davis Co.

phenicol and penicillin was effective at a lower concentration of each drug than was the inhibitory concentration of either drug alone. In 2 instances (Cases 19 and 11) a definite synergism was observed. In only 1 instance (Case 22) did the addition of chloramphenicol make a higher concentration of penicillin necessary for the inhibition. The difference in this instance was within the range of error of the tube-dilution method[13].

B. Clinical Response. Five of the 13 patients to whom chloramphenicol

TABLE 1.—THE SENSITIVITIES TO PENICILLIN, CHLORAMPHENICOL AND THE COMBINATION OF PENICILLIN AND CHLORAMPHENICOL OF STRAINS OF PROTEUS ISOLATED FROM 21 CASES

Inhibitory concentration in mcg./cc.	*Penicillin*	*Chloramphenicol*	*Penicillin and Chloramphenicol**
.22			
.22	15‡, 16		15, 16
.38			
.45			
7.5		16	
9	6, 14		6, 22
1.5			
1.8	22		1, 2, 5, 8, 14, 17, 20
3		15	
3.7	2, 8		4, 7, 10, 11, 12, 19, 23
6		1, 4, 5, 7	
7.5	1, 23		9, 21†
12		6, 9, 20, 23	
15	7, 10, 17, 21		
25		12, 14	
30	5, 19		
50		2, 8, 10, 17, 19	
60			
100		22	
100	4, 9, 11, 12, 18, 20	11, 18 21,	18

* The dot above represents the concentration of penicillin and the dot below the concentration of chloramphenicol.

† Thus the organisms from case 21 was inhibited by 7.5 mcg./cc. of penicillin combined with 12 mcg./cc. of chloramphenicol.

‡ Each numeral refers to a case which is designated by the same number in Table 2.

TABLE 2.—RESPONSE OF 23 CASES OF PROTEUS INFECTIONS TO PENICILLIN–CHLORAMPHENICOL THERAPY

Responded to chloramphenicol	*Responded to penicillin*	*Responded to chloramphenicol and penicillin*	*No response to chloramphenicol and penicillin*	*No response to chloramphenicol*	*No response to penicillin*	*Patient received aureomycin previously*
2, 3, 4, 17, 21	6, 9, 14	10†, 11, 22, 23	1*, 7, 8, 12, 13, 18	1, 5, 8, 10, 11, 12, 13, 19, 23	1, 4, 5, 8, 10, 12, 13, 15, 17, 18, 19, 22	1, 2, 5, 7, 8, 10, 12, 14, 16, 17, 19, 20, 21, 22
Total 5	3	4	6	8	12	14

* Responded to combination of penicillin, chloramphenicol and streptomycin.

† Each numeral refers to a separate case. Thus case 10 did not respond to penicillin or chloramphenicol but did respond to the combination of the 2 drugs.

was administered showed a satisfactory clinical response and 3 of 15 individuals who were given penicillin responded satisfactorily (Table 2). Six patients were treated with the combination of penicillin and chloramphenicol and in 4 of these, sterile urine resulted (Table 2.) Two of these 4 subjects (Cases 10 and 23) had not been affected by either drug when used alone (Table 2). Thus in 12 of 23 cases chloramphenicol and penicillin used singly or in combination were effective in the treatment of urinary tract infections caused by *Proteus* organisms (Table 2). Fourteen of the 23 subjects had received aureomycin within 3 weeks before the *Proteus* organisms were cultured from their urine (Table 2).

CORRELATION OF IN VITRO AND CLINICAL RESULTS. In one of the cases that responded to penicillin (Case 9) infection was caused by a strain of *Proteus* that grew *in vitro* in a concentration of penicillin greater than 100 mcg./cc. (Tables 1 and 2). In 2 cases (Cases 10 and 23) that responded to the combination of penicillin and chloramphenicol after each of these drugs when used alone had failed, infection was caused by strains that were more sensitive to the combination of the 2 drugs than to either drug alone (Tables 1 and 2). On the other hand, in 4 instances (Cases 1, 7, 8, and 12) in which *in vitro* tests showed that the combination of penicillin and chloramphenicol had increased effectiveness, there was no clinical response to their combined use (Tables 1 and 2).

Discussion. The reports of Jawetz[4,5,6] and his collaborators have stressed the fact that *in vitro* and in mice chloramphenicol as well as aureomycin, terramycin, and sulfadiazine decrease the rate of the bactericidal action of penicillin. In these same reports this group of workers showed that combinations of chloramphenicol, aureomycin, and terramycin with penicillin increase bacteriostatic activity and eventually sterilize cultures more effectively than do these drugs used alone[4,6]. Whether their findings suggest that chloramphenicol, aureomycin, and terramycin should be used with penicillin or whether they indicate that these drugs should not be used together depends on whether it is the rate of bactericidal activity or the bacteriostatic effect and eventual bactericidal result that determines the clinical efficacy of antimicrobial drugs. Ehrlich's[3] demonstration that spirochetes when exposed to salvarsan remained alive but lost virulence was the first indication that drugs did not have to kill bacteria to be effective therapeutically. The effectiveness of antibiotics that are primarily bacteriostatic, such as aureomycin, is further evidence of the fact that bacteriostasis is often all that is necessary for satisfactory clinical results. In addition the evidence presented in this report and the work of Spies *et al*[10], who reported a case of subacute bacterial endocarditis that responded to aureomycin and penicillin when neither drug alone was effective, suggests that in certain instances both chloramphenicol and aureomycin may be used with penicillin. Final judgment will have to await further clinical trial but at present it would seem that there is no contraindication to the use of aureomycin, chloramphenicol, or terramycin with penicillin in selected cases.

The lack of close correlation between the *in vitro* sensitivity tests and the clinical results should serve to emphasize the limitations of this procedure as a guide to therapy. While sensitivity tests have proved valuable aids in the treatment of problem cases by indicating the antibiotic or combination of antibiotics to which the causative organism was the most sensitive,

the foregoing results point out the fact that patients should not be denied possible beneficial therapy solely because of the results of *in vitro* determinations[5].

Summary and Conclusions. Many strains of *Proteus* organisms showed *in vitro* sensitivity to the action of penicillin and chloramphenicol. An additive as well as synergistic effect was observed when the 2 antibiotics were combined.

Twenty-three cases of *Proteus* infection were treated with either chloramphenicol, penicillin, or the combination of the 2 agents. Five cases responded to chloramphenicol, 3 cases responded to penicillin, and 4 cases responded to the combination of the 2 agents. Five cases showed no response to the combination of chloramphenicol and penicillin in spite of the apparent *in vitro* sensitivity of the causative strains. Thus penicillin as well as chloramphenicol, gantrisin, and neomycin may be considered as agents effective against some infections due to *Proteus* organisms. In addition, the combination of penicillin and chloramphenicol in certain instances may cure infections that have not responded to either medication given alone.

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THE PLASMA ANTITHROMBIN DETERMINATION: A NEW TEST FOR CANCER OF THE PANCREAS ASSOCIATED WITH JAUNDICE

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THE diagnosis of pancreatic cancer is admittedly difficult in advanced stages and is rarely made during its initial stage. It is axiomatic that all palliative or potentially curative surgical procedures for pancreatic cancer are facilitated by early diagnosis. Presently applied pancreatic function tests, however, are not specific for cancer, and permit only presumptive preoperative diagnosis. An ideal test for pancreatic cancer would possess a diagnostic range paralleling the natural course of the disease. It is apparent that no such test has been presently available.

It is impressive that in this study elevated antithrombin levels in jaundiced individuals often suggested the diagnosis of pancreatic cancer prior to the development of severe pain, weight loss, or extensive liver metastasis. Marked elevation in antithrombin occurred in each of 11 patients with pancreatic cancer with jaundice of less than 4 weeks' duration. The classification of pancreatic cancer patients into 3 sharply differentiated groups was based upon distinctive antithrombin alterations which seemed to correlate with the duration of associated jaundice. It is the purpose of this study to report characteristic patterns of plasma antithrombin levels in patients with pancreatic cancer in varying stages of jaundice.

Material and Methods. 1. PLASMA ANTITHROMBIN TEST. *Method A: In Which the Source of Fibrinogen is Human Plasma.* The details of this procedure have been reported elsewhere[3]. In this test, the patients' defibrinated plasma is the test substance and standardized topical thrombin is the substrate. After varying intervals of incubation at 37°C., aliquots of the reaction mixture are added to fresh human plasma and the clotting times are recorded.

Method B: An Alternate Method. This method involves the use of Armour's Bovine Fibrinogen.

Preparation of Fibrinogen Solution. Two cc. of borate buffer (stock solution) are added to 18 mg. of Armour's Fibrinogen; the tube is shaken gently and allowed to stand at room temperature. Stock borate buffer is used as a solvent for the fibrinogen and possesses a mild bacteriostatic action. Each liter contains 11.25 gm. H_3BO_3, 2.25 gm. NaCl, and 4 gm. $Na_2B_4O_7.10H_2O$ in distilled H_2O. This solution has a pH of 7.75. Specific resistance equals 170 ohms at 21°C.

Standardization of Thrombin. Two cc. of isotonic saline solution are injected into the 1000-unit vial of Parke, Davis topical thrombin. To a 50-cc. flask containing 20 cc. of isotonic saline solution, 0.25 cc. of the thrombin solution are added. The flask is carefully surrounded by ice in a small beaker and allowed to stand for 15 minutes.

Test Procedure. Small test tubes, with rounded bottoms, 3 inches in length and 10 mm. inside diameter, are used in the test. Into each of 2 tubes 0.06 cc. of freshly prepared fibrinogen solution are carefully pipetted and allowed to stand at room temperature. Two other similar tubes, each containing exactly 0.9 cc. of standardized thrombin, are immediately surrounded by ice.

Defibrinated "unknown" plasma is next prepared by adding 0.4 cc. of standardized thrombin to 1 cc. of "unknown" plasma and

then removing the clot at the end of 10 minutes. As much fluid as possible is extracted from the clot by squeezing it against the side of the test tube. In like manner, defibrinated "normal" plasma is prepared by the addition of 0.4 cc. of standardized thrombin to 1 cc. of normal plasma and by removing the clot at the end of 10 minutes.

The clotting time of the "unknown" defibrinated plasma is tested as follows: 0.2 cc. of the defibrinated plasma are added to the previously measured 0.9 cc. of the chilled standardized thrombin and the reaction mixture is incubated in a water bath at 37° C. At the end of 5 minutes incubation in a water bath at 37°C., 0.2 cc. of the above reaction mixture are added to 1 of the tubes containing 0.06 cc. of fibrinogen solution and the clotting time is accurately determined. The end point is reached when a strand of fibrin can be drawn above the reaction mixture. The appearance of this fibrin strand is *preceded* by a distinct cloudiness of the reaction mixture and is *followed* by the formation of a solid clot. Gel formation due to the citrate employed occasionally occurs 5 to 10 seconds following the addition of 0.2 cc. of reaction mixture to fibrinogen. These "false fibrin strands" are not *preceded* by cloudiness of the solution and are never *followed* by solid clot formation. (All time intervals are determined with the aid of a stop watch.) In similar manner, the clotting time of "normal" plasma is determined. Thus 0.2 cc. of defibrinated "normal" plasma are added to 0.9 cc. of standardized thrombin which has been kept chilled. After incubating 5 minutes at 37°C. in a water bath, 0.2 cc. of this reaction mixture are added to 0.06 cc. of the prepared fibrinogen solution and the clotting time is accurately determined.

The normal clotting time at the 5-minute incubation period ranges from 40 to 50 seconds.

An *elevated* antithrombin titer in jaundiced patients with pancreatic cancer is defined as one in which the clotting time of the unknown sample at the 5-minute incubation period must be at least 50% greater than that of the normal control.

A *decreased* antithrombin titer is defined in terms of the per cent decrease in clotting time of the unknown sample as compared with that of the control at the 5-minute incubation period.

Technique for Simultaneous Determinations of a Series of Unknowns. Five samples can be run simultaneously, that is, 1 normal or control and 4 unknowns, in the manner now to be briefly described.

At the zero hour 0.2 cc. of control defibrinated plasma are added to 0.9 cc. of standardized thrombin. Then, at 2-minute intervals, 0.2 cc. aliquots of each of the unknown defibrinated plasma are added to 0.9 cc. of standardized thrombin. At 10 minutes, 0.2 cc. of the control reaction mixture (normal defibrinated plasma plus thrombin) are added to a tube containing 0.06 cc. of fibrinogen and a clotting time is recorded. At 12 minutes the first unknown sample is run as follows: 0.2 cc. of "unknown" reaction mixture are added to 0.06 cc. of fibrinogen; at 14 minutes the next, and so on until determinations have been made on each sample after exactly 10 minutes of incubation for each.

With experience, it is possible to allow a 1-minute interval to elapse instead of 2 minutes between the addition of defibrinated plasma to standardized thrombin and in this way 9 tests can be run simultaneously. Running tests concurrently eliminates the variable of "thrombin drift".

Following this initial screening, a repeat determination is performed on each sample in which high or low readings were obtained. Clotting times are now made at 5, 10, and 15 minutes of incubation of both normal and unknown samples.

Fresh thrombin solutions are prepared daily and are kept at a temperature of 4°C. The fibrinogen solutions are also prepared daily but stand at room temperature.

2. Clinical Material. The plasma antithrombin level was determined on 261 jaundiced patients. The number of patients comprising each disease studied is listed in Table I.

Results. The results are summarized in Table 1.

Discussion. During the course of this investigation, 23 jaundiced patients with pancreatic cancer were studied. In each of 11 such patients with jaundice of less than 4 weeks' duration, remarkably high antithrombin levels were obtained. The antithrombin titers in the remaining 12 pancreatic cancer patients were normal in 6 patients, jaundiced for less than 4 months, and depressed in 6 patients, jaundiced for at least 4 months (Fig. 1). The overall pattern of antithrombin response, ranging from high levels in cancer cases with early jaundice to low levels in jaundiced cases of longer standing, conforms with the underlying patho-

logic physiology and natural course of progressive pancreatic cancer[1].

Kaplan and Angrist have demonstrated the mechanism by which obstruction of the common bile duct develops in cases of carcinoma of the head of the pancreas[7]. They pointed out 3 factors involved in obstruction of the biliary tract by carcinoma: 1) invasion of the wall and fixation and compression of the common bile duct by the tumor mass; 2) invasion of the common duct, a scirrhous reaction, and annular stenosis; and 3) invasion of the common bile duct and filling of the lumen by neoplastic tissue. In each of 39 patients reported, some fixation of the duct was necessary for the development of obstruction by mechanical compression, with resultant jaundice.

During the first few weeks following the initiation of this obstructive mechanism, the secretion of pancreatic

TABLE 1.—THE ANTITHROMBIN LEVEL IN 261 JAUNDICED PATIENTS

Diagnosis	*No.*	*Normal Antithrombin*	*Elevated Antithrombin*	*Low Antithrombin*
Cancer of the pancreas. Duration of jaundice less than 1 mo.	11	0	11	0
Cancer of the pancreas. Jaundice longer than 2 mo. Little or no metastasis	6	6	0	0
Cancer of the pancreas. Jaundice longer than 4 mo. Extensive metastasis to liver	6	0	0	6
Primary biliary cirrhosis	6	6	0	0
Infectious hepatitis	19	18	0	1
Post-necrotic scarring	9	9	0	0
Cirrhosis, with advanced liver failure	28	0	0	28
Cirrhosis, mild hepatic decompensation	46	46	0	0
Primary cancer of liver	3	0	0	3
Extensive metastatic disease of liver	4	0	0	4
Metastatic cancer, porta hepaticus	1	0	1	0
Acute pancreatitis	4	0	4	0
Chronic relapsing pancreatitis (in relapse)	2	0	2	0
Biliary tract disease	113	109	4	0
Acute cholecystitis	98	94	4	0
Common duct stone	6	6	0	0
Acute suppurative cholecystitis	5	5	0	0
Stricture, common bile duct	4	4	0	0
Cancer of undetermined origin	1	1	0	0
Hodgkin's disease	1	1	0	0
Gumma, liver	1	1	0	0

enzymes is still actively operative. As a direct result of mechanical pancreatic duct obstruction, plus uninterrupted acinar secretion of enzymes, the intraductal secretory pressure rises until parenchymal extravasation of enzymes must occur, and an acute interstitial pancreatitis is produced. This is the pathophysiologic basis for the finding of elevated antithrombin levels during these first few weeks of jaundice in pancreatic cancer. In a previous study, we reported markedly elevated antithrombin titers in 50 of 55 acutely ill, non-icteric patients (91%) with acute interstitial and necrotic pancreatitis[4,5]. It appears, therefore, that jaundiced individuals having antithrombin titers in the pancreatitis range may have pancreatic cancer, and should be followed from that standpoint.

Following the initial stage of interstitial pancreatitis with associated high antithrombin levels, a healed stage ensues[5]. Areas of pancreatic fibrosis and invading neoplastic tissue finally replace foci of exudative infiltration. It is precisely during this healed stage that normal antithrombin titers became evident in 6 pancreatic cancer patients with jaundice ranging from 1 to 4 months. The continued replacement of pancreatic acini, ducts, and stroma by fibrosis and neoplastic tissue, however, plus the additional variable of extensive liver metastasis, prepares the setting for the appearance of the end stage characterized by low antithrombin titers. It is our belief that the liver plays a critical role in the production of lowered antithrombin levels. It is conceivable that the extent of malignant hepatocellular replacement must be considerable before this change occurs[2,6].

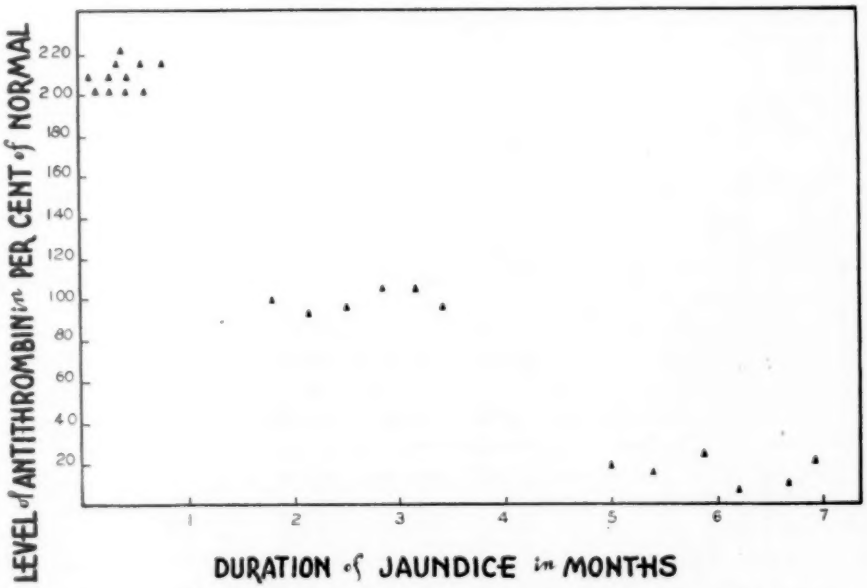

FIG. 1.—The plasma antithrombin level in 23 patients with pancreatic cancer.

Biliary tract disease causes the main stumbling block in the differential

TABLE 2.—CORRELATION OF ANTITHROMBIN LEVELS WITH THE NATURAL COURSE OF CANCER OF THE PANCREAS

	Original location, tumor	*Duration of jaundice*	*Metastasis*				*Peripheral venous thrombosis*	*Antithrombin titer*
			Regional nodes	*Root of mesentery*	*Perineural lymphatics*	*Liver*		
I. STAGE OF INJURY Rapid invasion; stage of interstitial pancreatitis	Ampulla	4–5 weeks	+	+	+	0	0	High
	Lower end of the common duct	4–5 weeks	+	+	+	0	0	High
	Head of pancreas; early fixation of duct	4–5 weeks	++	++	++	+	0	High
	Head or body of pancreas; no fixation of duct	None	++	++	++	+	0	Probably high Rarely performed in this unrecognized stage
II. STAGE OF ADAPTATION (Progression of tumor mass) Stage of healed pancreatitis	Ampulla	2–4 months	++++	++++	++++	++	0	Normal
	Lower end of the common duct	2–4 months	++++	++++	++++	++	0	Normal
	Head of pancreas	2–4 months	++++	++++	++++	++	+	Normal
	Body and tail of pancreas	2–4 months	++++	++++	++++	++	+++	Normal
III. STAGE OF EXHAUSTION Pancreatic insufficiency; cachexia; widespread metastasis	Ampulla	Over 4 mos.	++++	++++	++++	++++	++	Low
	Lower end of the common duct	Over 4 mos.	++++	++++	++++	++++	++	Low
	Head of pancreas	Over 4 mos.	++++	++++	++++	++++	+++	Low
	Body and tail of pancreas	Over 4 mos.	++++	++++	++++	++++	++++	Low

diagnosis of pancreatic cancer associated with jaundice. It is noteworthy that normal antithrombin titers were observed in 109 of 113 patients with biliary tract disease (Table I). It is postulated that the 4 positive cases represent secondary acute pancreatitis, perhaps on the basis of a common ampullary channel. In each of these 4 patients, however, the underlying gallbladder disturbance was of major importance and was at once apparent.

The presence of depressed antithrombin titers in each of 3 patients with primary liver cancer is of interest. Each tumor was massive, with extensive parenchymal invasion. It is apparent that low antithrombin titers observed in primary liver cancer occur during a late stage of the disease.

It should be stressed that the presence of high antithrombin titers in pancreatic cancer patients with early jaundice does not necessarily imply localization of the tumor, absence of liver metastasis, or operability of the lesion, although in each patient of the present study with early jaundice such correlation did exist. Our present number of cases is too small to warrant definite conclusions as to the correlation between the period of jaundice, alterations in antithrombin levels, and the size or operability of the pancreatic lesion. The only warranted conclusion is that elevated antithrombin titers may appear during the first 4 weeks of jaundice associated with pancreatic cancer. In this study, extensive liver metastasis and low antithrombin levels occurred in pancreatic cancer patients with jaundice exceeding 16 weeks' duration. It is significant, however, that regardless of prognostic implications, the diagnosis of pancreatic cancer appears to be supported by the co-existence of early jaundice and elevations in antithrombin.

In a discussion of pancreatic tumors Parsons[8] has recently stated, "Jaundice appearing early in the development of pancreatic cancer is the one hopeful element in an otherwise rather gloomy picture." It is interesting that, from the surgical standpoint, valuable information was derived from antithrombin determinations in pancreatic cancer patients with jaundice of recent origin. Since both ampullary tumors arising in either duodenal or terminal common duct epithelium, and true pancreatic tumors close to the ampulla cause jaundice early in their development, antithrombin determinations in these instances led the way to proper diagnosis and appropriate surgical management with a minimum of delay.

The antithrombin level is correlated with 3 stages in the natural course of pancreatic cancer (Table 2). It is of interest that peripheral venous thromboses, idiopathic thrombophlebitis, and thromboembolic phenomena were encountered in 11 patients (48%) in Group 3, in 4 patients (19%) in Group 2, and were entirely absent in Group 1. Whether decreasing antithrombin levels (correlating with clot-promoting tendencies) represents failure of a naturally occurring thrombin inactivation mechanism, is a study now in progress in our laboratory.

Summary. 1. The plasma antithrombin titer was determined in a series of 261 jaundiced patients.

2. Markedly elevated antithrombin levels occurred in each of 11 pancreatic cancer patients with jaundice of less than 4 weeks' duration. It is of interest that the appearance of elevated antithrombin titers coincides with the optimal period for surgical intervention.

3. Low antithrombin titers were observed in 1) patients with pancreatic

cancer plus extensive liver metastasis, 2) patients in severe liver failure, and 3) patients with massive primary cancer of the liver.

4. Normal antithrombin levels were obtained in 109 out of 113 patients with obstructive jaundice due to acute biliary tract disease.

Addendum: Since submitting this paper for publication we have studied 4 additional patients, each jaundiced less than 4 weeks, with antithrombin titers in the cancer range. Each diagnosis, cancer of the head of the pancreas, was confirmed at operation.

An additional patient, jaundiced for 3 weeks following metastatic spread to the porta hepatis from a rectosigmoid primary tumor, had elevated antithrombin titer levels. This is the second patient in our present series, therefore, demonstrating elevated antithrombin titers in metastatic disease of the porta hepatis (see Table 1). In each instance, however, autopsy revealed metastatic involvement of the pancreas, plus invasion of the porta and rather extensive involvement of the regional nodes.

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SURVEY OF EPIDEMIC TYPHUS ANTIBODY LEVELS IN BLOODS OF INDIVIDUALS BORN IN EASTERN AND CENTRAL EUROPE AND THE UNITED STATES

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Several reports published in the last 20 years[1,3-5] have confirmed Zinsser's hypothesis[7] that Brill's disease represents a recrudescence of an old infection with *Rickettsia prowazeki*. The disease is most common among people born in Eastern and Central Europe where such infections have been very prevalent. It is assumed that the rickettsiae persist in latent form in the body of individuals recovered from the disease. Although rickettsiae have been isolated in Brill's disease, their presence has not been determined during the quiescent period between the original infection and recrudescence. The survival of viral and rickettsial agents in the host is often associated with the persistence of demonstrable antibodies. Thus, although the finding of specific antibodies cannot be regarded as absolute proof of the coexistence of the rickettsiae somewhere in the body, the finding of a higher frequency distribution of such antibodies in individuals of European birth than in individuals born in this country would add strong support to this assumption, provided the 2 groups were derived from similar socio-economic segments of the population in this country. The chances of contact with typhus rickettsiae in the United States are probably the same in immigrants and native born persons of similar socio-economic groups. It was felt that a mass serologic survey of a number of consecutive hospital ward admissions might answer the question of the presence of typhus antibodies in the 2 groups. The place of birth of these patients was not known to the laboratory until the tests were completed. In addition to the 2 groups, a third control series was inincluded in this survey. This group consisted of inmates of a penal institution and a small number of doctors on the staff of a general hospital.

Materials and Methods. Serum samples were tested in the complement fixation test according to the method previously described[6]. Epidemic and murine typhus rickettsial ("soluble") antigens were obtained from a pharmaceutical company.* "Washed" rickettsial antigens** were also used. All sera were first tested in 2 dilutions (1:4 and 1:16). Many were subsequently retested in multiple two-

* The authors desire to express their thanks to the Lederle Laboratories for supplying the rickettsial antigen material used in this study.

** Obtained through the courtesy of Dr. Herald R. Cox, Lederle Laboratories.

fold dilutions. On several patients 2 sera were tested.

Results. Table 1 shows the results of complement fixation tests with both types of antigens. Reactions were noted in the sera of 16 individuals; 13 of these were born in Europe. One of these individuals, (J. C. C.) in the physicians' group, was born in Europe but also received typhus vaccine while in the Army. Among the American born persons, one, (J. H.), was known to have been vaccinated against epidemic typhus during World War II; 2 in the group of 92 prisoners served with the United States Army in Europe and may have received typhus vaccine, and the fourth, a ward admission, was found to have no complement fixation antibodies on repeated testing. Several comparative tests with the "soluble" and "washed" antigens are shown in this table as well as in Table 2. The results are compatible with what has been reported previously[2,4] on the greater specificity of the "washed" antigens. Nevertheless, as these results indicate, the "soluble" antigens were found to be quite satisfactory in the diagnosis of Brill's disease and also for the purposes of the serologic survey. The results of the survey, although showing reactions in low dilutions, appear to be specific. Thus, 12 of 69 individuals (17%) born in Eastern Europe gave positive results, whereas none of 80 (0%) born in this country possessed typhus antibodies. In the other groups (physicians and prison groups) there were no reactions except as noted above. Thus, antibodies to *Rickettsia prowazeki* persist in at least low concentration many years after infection.

An opportunity presented itself for the determination of the serologic pattern in 2 persons who recovered from Brill's disease. These findings are shown in Table 3. It appears that although there was a considerable decrease in antibody titer at the end of a year, antibodies were still present in significant amount after at least 20 months.

Discussion. In a group of 80 individuals born in this country who were admitted to the wards of the Jewish Hospital of Philadelphia with various complaints, there was not 1 who showed complement fixation antibodies to the rickettsia of epidemic typhus. In a group of 69 individuals of a similar age distribution and socio-economic background, but who were born in Eastern Europe, 12 (17%) possessed such antibodies. Some of these persons remembered having typhus many years ago in Europe; others stated that they did not recall having this disease or that they never had it. The length of their residence in the United States varied from 28 to 53 years. If one should accept the positive answers about history of typhus in Europe, the time elapsed since the infection varied from 30 to 58 years. In the absence of evidence of infection with *Rickettsia prowazeki* in this country—as shown by the group of native born persons (a serum of a 17-year-old daughter of B. T., born in this country, was also negative in the complement fixation test)—the results indicate that antibodies to *Rickettsia prowazeki* may persist in low concentration many years after infection. Brill's disease occurs primarily in persons born in Central and Eastern Europe who had apparently experienced such infection. The serologic findings in this group, 17% yielding positive results, are consistent with survival of rickettsia of the epidemic typhus for many years after infection. In the third series, consisting of 2 different socio-economic groups, the serologic results were in conformity with the findings in the second group. Two of 9 physicians

TABLE 1.—POSITIVE RESULTS OBTAINED WITH RICKETTSIAL COMPLEMENT FIXING ANTIGENS

Initials	*Sex*	*Age*	*History of typhus*	*Place of birth*	*Arrival in U. S.*	*Soluble antigens*		*Washed antigens*	
						Epidemic	*Murine*	*Epidemic*	*Murine*
M. F.	M	50	?	Roum.	?	8	4	4	<2
S. G.	F	73	No	Russ.	1920	4	2	nd	nd
D. P.	M	59	No	Russ.		8	4	2 or 4	<2
L. B.	F	63	?	Russ.	?	4 or 8	<2	2 or 4	<2
R. C.	F	69	?	Russ.	?	2 or 4	<2	2	Neg. in undil.
J. G.	M		1919		1922	4	<4	nd	nd
S. T.	M	71	No	Russ.	1897	2 or 4	2 or 4	nd	nd
B. T.	F	42	1920	Russ.	1921	8 or 16	<2 or 2	8 or 16	<2
W. T.	M	72	?	Russ.	1907	2	2	<2	<2
M. D.	M	68	1892	Russ.	1908	8	4	nd	nd
M. L.	F	60	?	Russ.	?	4	<2	nd	nd
I. C.	F	75	No	Russ.	1912	4	2	nd	nd
J. H. (Phys.)	M	24		U. S.		8	<2 or 2	16	<2
J. J. C. (Phys.)	M	43		Poland		2	<2	2	<2
45P	M	Served in U. S. Army in European Theatre—No information on vaccination				2 or 4	<2	4	<2
51P						<2 or 2	<2	Partial up to 1:4 or 1:8	<2

TABLE 2.—COMPARATIVE TITRATIONS OF STRONGLY REACTIVE BRILL'S DISEASE SERA WITH "SOLUBLE" AND "WASHED" RICKETTSIAL ANTIGENS IN THE COMPLEMENT FIXATION TEST

	1 Hour Test				*18 Hour Test*			
	"Soluble"		*"Washed"*		*"Soluble"*		*"Washed"*	
	Epidemic	*Murine*	*Epidemic*	*Murine*	*Epidemic*	*Murine*	*Epidemic*	*Murine*
81 S_2	2048	512	2048	512	2048	1024 (512)	2048	512
674 S_3	512	256	512	64	1024	512	1024	nd
1589 S_2	nd*	nd	nd	nd	4096	2048	8192	512
Guinea pig immunized vs. murine typhus	nd	nd	nd	nd	64	256	64	512

* nd = not done

TABLE 3.—PERSISTENCE OF ANTIBODIES FOLLOWING BRILL'S DISEASE

No.	*Date of illness*		*Reaction with "Soluble" epidemic and murine typhus antigens*				
			1/24/49	1/27	2/2	2/6	1/18/50
81	1/18/49	E	512	2048	2048	2048	16 or 32
		M	128	1024	1024	512	8 or 16
			4/30/49				Dec. 1950
1589	4/17/49	E	4096				256
		M	2048				64

possessed antibodies. One was born in Poland and was also vaccinated against typhus; the other, born in the United States, was also vaccinated. Only 2 of 92 inmates of a penitentiary gave some reaction; these 2 had spent some time in Europe with the United States Army and might have been vaccinated against epidemic typhus. The data presented point again to the greater specificity of the "washed" antigens. It was found, however, that the "soluble" type antigens, which are easier to prepare and which cost less than the purified antigens, were satisfactory in the survey and very helpful in the diagnostic serologic tests on 3 cases of Brill's disease[1].

Summary. 1. In a group of 69 individuals born in Eastern Europe, 12 (17%) possessed antibodies to epidemic typhus rickettsia, whereas in a group of 80 individuals of a similar economic background but who were born in this country, none possessed these antibodies.

2. In a group of 92 inmates of a penitentiary, only 2 showed these antibodies, and it is possible that these resulted from vaccination to typhus.

3. The definite correlation between the presence of antityphus antibodies and residence in Eastern and Central Europe implies that these antibodies represent previous infection with epidemic typhus. The long persistence of these antibodies after the individuals leaving an area where typhus is prevalent is consistent with the survival of rickettsia in latent form for long periods of time after the original infection.

4. The washed rickettsial antigen was again found to be more specific than the soluble antigen. Nevertheless, the soluble antigens were found to be of great value in the diagnosis of Brill's disease and also for the purpose of this survey.

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PROGRESS
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UNDER THE CHARGE OF

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ERYTHEMA NODOSUM

A Survey of Some Recent Literature

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FOR many years the nosologic status of erythema nodosum has been an enigma. In spite of a vast literature, the etiologic concept of this disease is still a matter for debate. Because of this extraordinary interest in a cutaneous process by physicians other than dermatologists; because of the variety of often contradictory opinions held in various countries regarding its nature; because erythema nodosum represents an outstanding example of the intangible borderline between dermatology and internal medicine; and because it illustrates how far the dermatology of today has progressed from the descriptive dermatology of 50 years ago, we believe a concise review of some of the recent literature on this subject is in order. The current medical interest in erythema nodosum is indicated by the long editorial on the subject in the Journal of the American Medical Association of December 30, 1950[18], and several recent monographic presentations.

The designation, erythema nodosum, was introduced by the English dermatologist, Wilan[88], as part of a general discussion of the varieties of erythema. In 1860 Hebra[37] separated erythema nodosum from the erythema multiforme group, and advanced the view, now being revived, that erythema nodosum is a specific disease. His description of erythema nodosum has been adopted by subsequent authors, and according to Löfgren's[51e]

translation, the lesions of erythema nodosum are:

"Light-red raised nodules, either round-topped or oval in shape, tender to the touch, and mainly situated on the legs. In many cases the eruption is preceded by a slight temperature elevation or even chills; often, however, the patient has no previous warning of the disease before he sees or feels the nodes. They occur as a rule in various sizes, the smallest the size of a pea and the largest of a closed fist. The individual nodules are usually discrete, and at first pale red with a faint gold tinge; at a later stage they turn dark red, then livid, and after the redness has disappeared the lesions persist for a long time in the form of yellowish pigmentation. These shiftings of color are the same as those occurring after a bruise, and for this reason the name dermatitis contusiformis has been used by some authors."

The diagnosis of erythema nodosum is usually easy, but difficulty may be experienced in cases with aberrant forms such as lesions on the face[40,72,84b] which resemble urticaria or erythema multiforme.

Since these early days numerous studies and reviews of this subject have appeared. Among them are the publications of Tachau[80], Rotnes[67], Symes[79], Lendon[48], Ernberg[21b], Keil[45b], Forman[29], Wallgren[84b], Löfgren[51e], Hellerström[39], Spink[72], Favour and Sosman[26], Collis[14], Skiöld[69], Rollof[66], Holmdahl[40], and Johnson, Hanson and Good[43]. Other works will be referred to specifically later.

Etiology. Erythema nodosum has been considered to be 1) a specific disease, 2) a sign of tuberculosis, 3) a manifestation of rheumatic infection, 4) an infection with Beta hemolytic streptococci, 5) a nonspecific allergic reaction, 6) a nonspecific indication of various causative factors of toxic type, 7) or concurrent infections. Adherents to each point of view have been numerous and to assemble the evidence for the various facets of this etiologic puzzle would require more space than is available or even warranted. Accordingly we shall note the essential thoughts on erythema nodosum as provided by certain recent studies. In no sense, therefore, is this a complete survey.

Before submitting detailed arguments, certain generalizations regarding the possible cause of erythema nodosum may be stated. Although unfortunately, they are based upon studies usually embodying small numbers of cases, they do illustrate the complexity of the problem involved in deciding what may be the actual basis for erythema nodosum. In the first place, studies from different localities and at different times suggest that the etiologic factors may differ to a great degree according to geographic location. For example, although in 1930 there was a definite tendency to accept the tuberculosis cause of erythema nodosum in this country (tuberculosis is the generally accepted background in Scandinavia)[15], the most recent study by Johnson, Hanson and Good[43] from the Mayo Clinic tentatively concludes that pulmonary hilar adenopathy may be an associated manifestation of erythema nodosum and not due to tuberculosis, sarcoidosis or coccidioidomycosis. In these cases disappearance of the hilar enlargement probably may be anticipated as the erythema nodosum subsides. This same trend away from tuberculosis as the outstanding cause in children in the United States was expressed earlier by Lincoln, Alterman and Bakst[50].

The rheumatic fever cause of erythema nodosum is still favored by

some, in spite of the fact that as Keil[45a] pointed out in 1937, in the late 19th Century, when several of the classic works on rheumatic fever were written, the concept of this disease was not clear. As a result of ill-defined diagnostic criteria, many patients with joint pains were incorrectly considered to have rheumatic fever. Since erythema multiforme and erythema nodosum are often associated with joint pains and a slight fever at their onset, they were considered specific aspects of rheumatic fever. Although there are cutaneous lesions of rheumatic fever which in a general way resemble erythema nodosum and erythema multiforme, cases of true erythema nodosum associated with rheumatic fever or evidence of cardiac disease, or vice versa, are so few that the relationship of the erythema nodosum to rheumatic fever cannot be established with any degree of certainty. In addition, Favour and Sosman[26] from Boston studied the clinical features of erythema nodosum in 155 patients, 61 of whom were followed for 1 to 20 years. Their findings led them to reject the rheumatic fever cause, but they felt that erythema nodosum is a hypersensitivity disease. Individual predisposition, a variety of infections and chemical agents, and local trauma contribute to its occurrence. Martens[54] also felt that constitutional differences may be responsible for the fact that erythema nodosum is not seen in all cases of tuberculosis or in response to other factors. Poppel and Melamed's[64] survey of 88 cases of erythema nodosum likewise indicated that the condition may be found during the course of various diseases, both infectious and noninfectious, virus, bacterial, chemical and toxic. It is evident that no common agent causes these diseases that might be expected to be the cause of erythema nodosum. In a small group of their patients (approximately 15%), no evident associated disease was present.

The variety of diseases with which erythema nodosum has been associated includes* leprosy[35,65]; trichophytosis[7]; syphilis[28,51e]; coccidioidomycosis[16,17,25,33a,b,70,89a,b]; respiratory infection with false positive serologic reaction[43,51]; streptococcic infections[62,63]; lymphogranuloma venereum[39a,72]; meningococcemia[55]; influenza[8]; measles[22,72,84d]; dental infections[20]; ulcerative colitis[1,12]; sarcoidosis[6,31,36,46,51e]; whooping cough[84d]; gonorrhea[15e]. Simpson[68], however, contends that there are only 4 cardinal types of infection which are associated with erythema nodosum to a significant degree, namely, primary tuberculosis, acute hemolytic streptococcal infection, coccidioidomycosis, and lymphogranuloma venereum. It may occur in patients suffering from any of these diseases, either spontaneously or in response to a "provocative agent." Of all "provocative agents," sulfathiazole is the most effective, and it is highly specific in that it provokes erythema nodosum only in the presence of the above-named processes.

On the other hand, drugs may, in addition to the provocative effect, induce erythema nodosum as a primary effect. These concepts will be elaborated on later.

Occasionally erythema nodosum may occur in a patient harboring more than one infection, thus exerting a combined effect. For example, erythema nodosum, although of an idiopathic or rheumatic nature, is more apt to occur in persons with tuberculosis[27,84a], or has an activating effect on latent tuberculosis[42,79a,84a]. Westergren and his colleagues[86,87] in a number of studies have further elaborated the idea of mixed infection or complex etiology for erythema nodosum.

* Only type references are given; the number of references on this phase is legion.

Although usually no particular distinction is made between children and adults in discussions of the causes of erythema nodosum, it is possible that age may play a role in this problem. This is especially the case in tuberculosis, since the infection is generally regarded as less significant in the adult.

Aside from the controversies dealing with the cause of erythema nodosum, there is considerable disagreement as to the actual pathogenesis of this problem. Eulenburg[23] as well as others[24,49] many years ago considered it to be a vasomotor neurosis. Others[9,82] for a long time have given support to the idea that erythema nodosum is an inflammatory reaction provoked by bacterial emboli. Still others have maintained that erythema nodosum is an allergic or hyperergic symptom[5,30,39b,56,90]. On the basis that erythema nodosum might be a manifestation of a hypersensitive state, Ureles and Kalmansohn[83] effected an immediate and striking response in a case of erythema nodosum with orally administered cortisone (cf. Farber and Mandebaum[25a]).

In the ensuing discussion we shall present data relating to the various etiologic concepts as presented in some of the pertinent recent literature. It must be reiterated, however, that in spite of the volume of the literature and the dogmatic attitude of some of the proponents of certain viewpoints, the actual cause of erythema nodosum is not known.

Erythema Nodosum as a Specific Disease. Since Hebra first thought erythema nodosum was a specific disease, numerous others during the latter part of the 19th and early part of the 20th centuries came to the same conclusion.

Although certain cases have been recognized as possibly being due to a specific infection or to drugs, these were considered apart as secondary or symptomatic erythema nodosum. The proponents of the specific disease concept based their assumption on the following characteristics of erythema nodosum (nodal fever, Lendon): contagiousness, epidemic occurrence, seasonal incidence, characteristic course (incubation period, prodromal symptoms such as sore throat, febrile reaction, eruption, convalescence and post convalescent immunity).

In recent years there has been a revival of interest in the specific disease concept of erythema nodosum[41,45b,78]. The most ardent recent advocate, Miescher[57], bases his opinion on the findings in 26 patients from the Medical Clinic of Zurich. Aside from 6 patients with typical primary tuberculous complex, the material was comprised of 9 with marked sensitivity to tuberculin, but with hilar adenitis, and 8 individuals with negative tuberculin reaction, one of which had deep trichophytosis. The remaining 7 had nonspecific diseases. In all of the specimens Miescher examined, he found a leukocytic inflammatory reaction, a large number of nodular granulomas, characterized by a radial and palisade-like structure. As the nodular formations are absorbed, giant cells develop. These nodules are identical, according to Miescher, with the lipophagic granulomas described in 1940 by Wallgren and Gnosspelius[85]. He believes the granulomas are evidence against the view that erythema nodosum is a pathologically uniform reaction of multiple etiologic background, but rather that it is a reaction to a virus. Erythema nodosum, according to Miescher, occurs along with tuberculosis in the same manner as herpes simplex occurs in patients with malaria, in menstruating women (recurrent) and the like.

Löfgren and Wahlgren[52] also studied the histopathology of erythema no-

dosum. Biopsies were made on 64 women, aged 17 to 72 years, with erythema nodosum of from 1 to 60 days' duration. In all groups, eruptions of the same duration showed essentially the same picture. Erythema nodosum in patients with sarcoidosis and with eruptions subsequent to sulfonamide therapy showed no difference from those lesions in patients not affected by these conditions. They found as typical of the eruption involvement of the subcutaneous tissue, fibrinoid degeneration within connective tissue septa, granulomatous foci of histiocytes and lymphocytes, giant cells of foreign body type, so-called "Wucherende Atrophie" of the adipose tissue and neural changes in the cutis. Contrary to Miescher, Löfgren and Wahlgren interpreted their findings as indicating an allergic origin for the eruption. On the other hand, Nubé[61], who found granulomas in 20 to 24 cases of erythema nodosum and none in 18 cases of erythema nodosum processes (erythema induratum; Darier–Roussy sarcoid; Weber–Christian disease), was inclined to agree with Miescher's viewpoint.

Winer[89b], in a well illustrated paper, has summarized the histopathology of nodose lesions of the lower extremities. From this it appears that erythema nodosum has a characteristic picture similar to periarteritis nodosa, in that, although the arterioles are stenotic, they function sufficiently to prevent some of the necrosis of the fat seen in erythema induratum. He details in a convenient table the differential histologic features of a variety of nodular diseases resembling erythema nodosum. In an earlier report on the nodose lesions of coccidioidomycosis, Winer[89a] concluded that the local clinical appearance and the histologic picture of erythema nodosum, whatever the cause, are the same. His observation is in accord with Brocq's[11] contention that the process is to be classified with the erythemas. The primary changes are vascular and place the disorder in the vasculitis group, as Montgomery, O'Leary and Barker[59] classified it.

Regardless of the merit of the specific disease interpretation of erythema nodosum, there are certain cases which do not fit into any of the etiologic classifications usually employed[32,43].

Erythema Nodosum, Rheumatic Fever and Streptococcic Infection. Although the idea that erythema nodosum was of rheumatic origin was suggested in 1855, it was not until 1886 that evidence which seemed to substantiate the theory that erythema nodosum is a rheumatic complaint was produced[53]. On the basis of study of the records from various London hospitals of 108 patients with nodal fever, MacKenzie concluded that erythema nodosum is frequently, if not generally, an expression of rheumatism even when no other definitely rheumatic symptoms are present. This view was accepted for several decades in England and the continent of Europe. The frequent association of sore throat and joint pains with erythema nodosum was the basis for this belief, but other authorities have denied that these symptoms actually are of rheumatic origin or that they are frequently associated with rheumatic fever.

The matter of the association of heart lesions with erythema nodosum is also a subject of great debate. Mackenzie[53] reported that 20 of his 108 patients presented heart lesions and that in all probability endocarditis developed in 5 cases during the attack of erythema nodosum. Although Mackenzie's diagnostic criteria have been questioned, Edström[19] found that in 23 of 48 patients with erythema nodosum and polyarthritis rheumatica

cardiac damage developed after the attack of erythema nodosum. In 8 other cases there were vague signs of endocarditis during their hospitalization. Other writers, notably Spink[72] and Poppel and Melamed[64], have found a lower incidence of cardiac damage in association with erythema nodosum, while still others have found none.

The trend of recent investigations on the whole is to deny the relationship of erythema nodosum to rheumatic fever. Feer[27] and Keil[45a], as previously noted, have been rather prominent in adducing evidence against this relationship.

The literature on this problem is fully covered in Löfgren's[51e] and Rollof's[66] reviews, but Favour and Sosman's[26] statement gives a good summary of the present status of this problem:

> "The tendency to classify erythema nodosum with the so-called hypersensitivity diseases (rheumatic fever, rheumatic states, polyarteritis nodosa, disseminated lupus erythematosus, glomerulonephritis and allergic purpuras) has clouded the relation of erythema nodosum and rheumatic fever to streptococcic infections. For instance, it has been noted that 11% of patients with erythema nodosum have preexisting rheumatic heart disease, that migratory polyarthritis may be present in both conditions and that occasionally a prolonged P-R interval in the electrocardiogram or the new development of rheumatic murmurs has accompanied erythema nodosum."

Undoubtedly rheumatic fever does occur with erythema nodosum, but as Favour and Sosman[26] as well as others have shown from their material, it is unusual.

There has also been considerable study of the relationship of Beta hemolytic streptococcal infection and erythema nodosum. Stone[77], Goldstein[34], and Pilot[62] were early American proponents of this view. Although their evidence consists of case reports, a number of authors have since taken up the task of trying to differentiate by cutaneous tests (Collis's streptococcal endotoxin, antistreptolysin reaction or titer) erythema nodosum of streptococcal or other cause. This effort has failed[44,51e].

Favour and Sosman[26], who cultured material from the throats of 55 patients, found no Beta hemolytic streptococci from 28 persons for whom material was cultured once, or from 2 for whom it was cultured twice. They were cultured one or more times from the remaining 25 patients. In material from several persons with recurring attacks of erythema nodosum they were cultured during attacks and could not be cultured in the intervals. Favour and Sosman[26] used a suspension of killed Beta hemolytic streptococci from the throats of patients with erythema nodosum or acute pharyngitis due to this organism in a concentration of 1,000,000,000 organisms per cubic centimeter as an antigen for skin tests. They noted two types of reaction, local (induration, edema and erythema beginning in 12 hours, maximal in 24 hours), and systemic (beginning in 5 to 12 hours with increased myalgia, arthralgias of knees and ankles, at times with swelling of the joints anorexia and elevation of temperature). Twenty-eight patients were studied with multiple tests on the skin. Fifteen of 17, in whom Beta hemolytic streptococci were demonstrated in their throats by culture, had a significant systemic reaction and an increase in nodes following the cutaneous test, but not following other cutaneous tests (brucellergen, lygranum or an alpha streptococcus vaccine). Eleven of the 13 other patients similarly tested gave

a positive local streptococcal reaction only. The residue of 4 of 15 patients, who had had systemic reactions at a later time when their disease was mild or subsiding, did not reproduce systemic reactions or nodes, but did cause local cutaneous reactions. The statement of these authors summarizes satisfactorily the present thought regarding streptococci in the causation of erythema nodosum. "Another sparsely documented cause of erythema nodosum is infection with Beta hemolytic streptococci. In this country sporadic cases have been reported. The culture of Beta hemolytic streptococci in material from the throats of patients with pharyngitis accompanying erythema nodosum and the induction of remote lesions in patients with erythema nodosum with intradermal injections of streptococcic broth filtrates or streptococcic nucleoprotein suggest that streptococci are nevertheless a common cause of the disease."

In connection with the bacterial causation of erythema nodosum it is of interest that Moon and Strauss[60] isolated organisms of genus *Corynebacterium* from the subcutaneous tissue of each of 3 cases of erythema nodosum (also from blood of 1 case of unusual severity). In 13 of 14, animals inoculated developed lesions with histologic characters of those of erythema nodosum. Some organisms recurred in cultures from these lesions. Similar organisms were also noted in sections from human and animal lesions (similar to Rosenow organisms?). Moon and Strauss suggested that the organism be called *Corynebacterium cutis nodosae*.

Erythema Nodosum and Tuberculosis. The relationship of erythema nodosum to tuberculosis has been discussed repeatedly in textbooks of dermatology and tuberculosis and in medical journals published in the United States and abroad. Most authors concluded that in adolescents and adults, the majority of cases seen in various parts of the United States would seem to be due to infection other than tuberculosis, while most of those from certain European countries are of tuberculous origin. However, even in certain European centers the tuberculous cause is accepted by some with a certain amount of skepticism[10].

The development of our present knowledge of the possible tuberculous nature of erythema nodosum is based upon a series of observations, beginning in 1872 when Uffelmann[81] suggested the connection between the two processes. In the pre-tuberculin and pre-Roentgen-ray days the diagnosis of tuberculosis was a matter of sheer guesswork. The numerous reports of investigations of this problem (summarized by Löfgren[51e], Rollof[66] and others) as recent as 1926, however, employing modern diagnostic procedures were based on too few and too selected cases to allow definitive conclusions. In spite of these deficiencies in the earlier material, the impression has been widespread in the British and Scandinavian countries that as high as 95% of the cases of erythema nodosum are tuberculous. The apparent discrepancies between the European and American viewpoints warrant a brief analysis of the more recent studies which may throw light on the actual status of this relationship. In assessing the value of the results, Rollof wisely points out that it is necessary to ascertain how representative of the general population the material is, and how far it consists of especially selected cases, since the occurrence of erythema nodosum among sanatorium patients will indicate that all patients with erythema nodosum have tuberculosis. Advances in the diagnosis of tuberculosis

have played a significant role in the developing knowledge, or lack of it, of the association of erythema nodosum with this disease. The importance of Roentgen-ray examination was first indicated by Kober[47] who observed a patient with hilar enlargement. Ernberg[21a] employed both Roentgen-ray study and tuberculin tests. In 35 of 39 of his patients there appeared to be a fresh tuberculous infection. Wallgren[84c,e] made numerous observations on the connection between the two processes. In 1926 he reported that practically all of the children who had developed erythema nodosum gave positive reactions to tuberculin. These patients had previously yielded negative reactions. In several series the tuberculin test was positive in from 95 to 100% of the cases. Other investigators felt the tuberculin test was not important, while still others, recognizing the possible nonspecificity of some reactions, believed the test was of high sensitivity and indicated a tuberculous background in erythema nodosum. Sometimes new lesions of erythema nodosum may be seen after performance of a tuberculin test (Chauffard and Troisier[13]).

Histologic examinations have not been of much help in determining the tuberculous cause of erythema nodosum and, as described above, the histologic picture, while characteristic of erythema nodosum of all causes, is not of tuberculous type. Autopsy in some cases failed to reveal tuberculosis anywhere.

Search for tubercle bacilli in patients with erythema nodosum has yielded equivocal results; some studies have produced positive findings, others negative, or still others have disclosed organisms other than the tubercle bacillus (see above). The bacteriologic methods employed included blood cultures, guinea-pig inoculations with involved tissue, and culture of gastric washings.

Newer studies of the tuberculosis–erythema nodosum problem by Löfgren[51g,h] reveal that in the cases of erythema nodosum collected in Stockholm between the years 1942 and 1946 there was in 58% an etiological connection with tuberculosis. Distribution according to age demonstrated a relationship between age and etiological type: 15 to 24 years: 78.1%; 25 to 34 years: 55.6%; and 35 to 44 years: 30.3% of tuberculous etiology. Distribution according to sex revealed erythema nodosum to be a disease of childhood in the male sex, while in women the maximum incidence was reached in the 15 to 24-year group. The material from 1942 to 1949 demonstrated, especially for the last 2 years, a significant decrease in the younger age-groups, namely, the groups where connection with tuberculosis is prevalent. This is attributed to the rapid fall in cases of tuberculous primary infections. It is assumed that this is due to the tuberculosis campaign with BCG vaccination and mass radiography, and perhaps also to a reduced infection risk as a result of chemotherapy and chronic tuberculosis.

Heimbeck[38], who studied 110 women with primary tuberculosis infection with erythema nodosum and 202 women who fell ill with symptoms of primary pulmonary tuberculosis without erythema nodosum, concluded that tuberculous erythema nodosum in women manifests an individual resistance which reduces the development of malignant pulmonary tuberculosis and hence the risk of tuberculous mortality in individuals with this symptom to a fraction of what it is without these symptoms.

In only 4 of Favour and Sosman's[26] 155 patients was there clinical evi-

dence of active tuberculosis coincident with erythema nodosum.

In a large study, Holmdahl[40] concluded that primary infections seem to be combined with erythema nodosum to about the same extent during the various periods of childhood, with the exception of the first years of life. On comparison of "invertors" (individuals whose negative tuberculin tests have become positive) with cases of primary tuberculosis accompanied by erythema nodosum, the risk of pleurisy and postprimary pulmonary tuberculosis seems to be greater among the patients with erythema nodosum. If cases of hilar adenitis with and without erythema nodosum are compared, it is not possible to demonstrate a significant difference. It seems that the symptoms of primary tuberculosis are similar in children and in adults, but with advancing age there are less pronounced primary changes. Healing is more rapid in older children, while the risk of the development of meningitis seems to be higher in cases with extensive hilar adenitis changes. Invertors with primary changes run greater risk of contracting pleurisy and pulmonary tuberculosis than invertors without primary changes. There is considerable risk of the development of postprimary tuberculosis in adults as well as in children, but the risk of meningitis seems to decrease with advancing age. The opposite seems to apply to postprimary pulmonary tuberculosis. It would appear that the risk of development of pulmonary tuberculosis is greater for invertors in adulthood than in earlier life. This is also the case in primary tuberculosis associated with erythema nodosum. Exudative pleurisy, except for first years of life, is a common complication in childhood as well as in adult life. The risk of incurring pleurisy following primary infection is somewhat greater in adults than it is in children. Holmdahl followed 657 patients with primary tuberculosis with erythema nodosum from birth to 16 years and found that 52.5% acquired their primary infection between birth and 7 years of age. Phlyctenulosis occurred in 6.5% of cases of erythema nodosum. The mortality from postprimary tuberculosis was greatest among those cases of primary tuberculosis which were the result of intrafamilial infection. In 537, unquestionable primary tuberculosis was present. Hilar changes were established in 94.7% and parenchymal pulmonary changes were established in 59.8%. Thirty-two patients (4.9%) died of tuberculosis, and in 147 (22.4%) one or several forms of postprimary tuberculosis developed. There were 17 cases of tuberculous meningitis, 1 case of miliary tuberculosis without meningitis, 83 cases of exudative pleurisy, 50 cases with certain and 17 cases with doubtful postprimary pulmonary tuberculosis. All of the patients in whom tuberculin tests were completed were still tuberculin-positive after a mean period of 14.5 years. There were 14 deaths from causes other than tuberculosis, and tuberculosis was not contributory to these deaths. The observed prognosis was less favorable in those cases of primary tuberculosis with erythema nodosum in which primary tuberculosis changes were demonstrable and in which the course of the primary changes or the rise in sedimentation rate was protracted.

Johnson, Hanson and Good[43], after a study of the literature including the reports of Skiöld[69], Spink[72] and others, report 9 cases in which pulmonary hilar adenopathy was present. No disease other than erythema nodosum was present which might be the cause of the erythema nodosum. Their tentative conclusions as to the hilar en-

largement being a part of erythema nodosum of more specific etiology seem reasonable. It would appear justifiable, therefore, to conclude that while the importance of tuberculosis as a cause of erythema nodosum is not established in adults, in children it is an etiologic factor the importance of which cannot be denied.

Drugs and Erythema Nodosum. Erythema nodosum has long been considered a drug eruption[2c], and has been thought of as an allergic reaction to a variety of medicaments, notably, iodides, bromides, salicylic acid, phenacetin, arsphenamine, and antimony. More recently many observers have reported on patients in whom erythema nodosum has appeared to be caused by sulfonamide drugs, especially sufathiazole. Allergy to the drug has been thought to be the modus operandi of the production of the eruption. There are observations which suggest that erythema nodosum, following sulfonamide therapy given for various infections, differs from the spontaneous type. This may indicate that a mechanism other than toxic from the drug alone is operative. This could perhaps be a simultaneous reaction of the organism against the infection under treatment.

Milian[58], Stokes and Cathcart[74], Stokes, Ruedemann and Lemon[76], and Stokes and Kulchar[75] in studies summarized in this journal[73] had suggested a similar explanation for the reactions to arsenicals beginning 30 years ago. Similar concepts in regard to sulfonamides and erythema nodosum were considered by Berglund and Frisk[4]. In 1943 Miescher[57b] studied 58 cases of cibazol (sulfamide thiazole) eruption, and suggested that these were not drug eruptions caused by sensitization, but rather had arisen as a result of the formation of allergic or toxic microbic products due to the medication. He did not, however, produce evidence of the existence of these infections. In several publications, Löfgren[51a,b,c,d] reported considerable material substantiating the idea that cases of so-called toxic erythema nodosum from drugs were in reality of infectious origin, the medicaments only playing the part of a provoking agent. He summarized the evidence for this idea from the literature, as follows:

"Brief mention will be made of some of the observations throwing light on the significance of such provocation factors in the occurrence of erythema nodosum (or in certain cases, erythema multiforme). Thus, erythema nodosum was observed after tuberculin tests in patients with early tuberculosis (Moro, Löfgren), injection of diphtheria anatoxin (Debre *et al.*, Löfgren), treatment of tuberculous lymphomas with Roentgen rays (Milian, Löfgren), acute nonspecific infections (Forman and Whitwell, Löfgren). As provacation factors in postprimary erythema nodosum Wallgren mentioned acute nonspecific infections, Segerstrale pneumothorax treatment, and Seidelin-Schnohr administration of bromides and sanocrysin.

"Erythema nodosum of streptococcal type was found to occur after treatment with sulfanilamide preparations (Löfgren, cf. Gsell, Berglund and Frisk). Just as Ernberg and many other investigators had observed recrudescence of freshly disappeared nodal fever efflorescences after turberculin injections in tuberculous cases, so Coburn and Moore, Spink, and Löfgren noted a similar recrudescence of the exanthem in streptococcal cases after injection of streptococcus allergen.

"Injection of Frei antigen (Hellerström, Sonck, Nicolas *et al.*, Bosn-

jakovic) provoked erythema nodosum in cases of lymphogranuloma inguinale, and a number of observers noted the exanthem after treatment of the inguinal lymphomas either by surgical means (Jersild, Goldberg and Fonde) or by Roentgen-ray treatment (Nicholas *et al.*, Sonck). Frei and Hoffmann observed nodal fever eruptions after medicinal treatment in lymphogranuloma inguinale.

"Bloch noted that erythema nodosum arose in patients with trichophytosis after injection of trichophytin, and Heden reported the same skin manifestations in a case of secondary syphilis after intravenous injection of luetin."

Two recent studies elaborating the provocation effect of the sulfonamides, especially sulfathiazole, in producing erythema nodosum, are those of Simpson[68] and of Rollof[66]. Both of these studies, but especially the latter, review the world's literature *in extenso*. Hence there is no need to mention the details here.

Simpson[68], whose work has been mentioned previously, described the provocation of erythema nodosum in patients with tuberculosis, lymphogranuloma venereum, coccidioidomycosis and acute hemolytic streptococcal infections. As stated, of all the agents capable of this provoking effect, none is as potent as the sulfonamide drug, sulfathiazole, and according to Simpson, "there is much evidence that with occasional apparent exceptions, administration of this drug is not followed by erythema nodosum when it is used in the treatment of other diseases." Furthermore, he pointed out that there is chemical and histopathologic similarity of "provoked" and "spontaneous" erythema nodosum. Simpson's personal experience with 1,050 cases of venereal disease in India, treated with sulfathiazole, "provides further evidence of (a) a close relationship between lymphogranuloma venereum and erythema nodosum, and (b) the strictly selective effect of sulfathiazole when it provokes this eruption."

Rollof[66], in an investigation of the significance of sulfathiazole in children mainly with reference to primary tuberculosis, studied 706 patients; 231 were tuberculous and 475 were nontuberculous. Of the latter, 98 were BCG-vaccinated and tuberculin-positive and the remainder were tuberculin-negative. All the nontuberculous patients had had some other infection for which they had been treated with sulfathiazole. Erythema nodosum following sulfathiazole therapy occurred in 129 cases of which 105 (81.4%) were tuberculous and 24 (18.6%) nontuberculous. Among tuberculous cases, sulfathiazole erythema nodosum occurred in 45.5%; among nontuberculous, it occurred in 5.1%. The difference is considered statistically significant. The incidence of erythema nodosum in cases of primary tuberculosis was higher when sulfathiazole was administered, either therapeutically or experimentally. The frequency of erythema nodosum following sulfathiazole therapy is inversely proportional to the duration of the tuberculous process. The more recent the process, the higher is the frequency. It could not be concluded with certainty that there was a relation between the development of erythema nodosum following sulfathiazole therapy and either the activity of the tuberculous process or the presence of "multiple infection", such as Beta hemolytic streptococci in the throat. There was no evidence that erythema nodosum resulted from hypersensitivity to sulfathiazole. Erythema nodosum can develop in association with treatment with other

sulfonamides, but frequently is low compared with that associated with sulfathiazole therapy. No difference was observed between the lesions of spontaneous erythema nodosum and those of erythema nodosum following sulfathiazole therapy, although in the latter the lesions clear up rapidly when the drug is discontinued without passing the color phases of the spontaneous type. Perhaps spontaneous erythema nodosum and erythema nodosum following sulfathiazole therapy are manifestations of an allergic phenomenon caused by some kind of infection, the sulfathiazole acting the part of a provocative factor but no evidence is presented to explain its action.

Erythema Nodosum and Certain Infectious Diseases. Besides the infectious and toxic agents which were discussed above in some detail, there are a number of diseases (mostly infections) which are associated with erythema nodosum with varying frequency.

Coccidioidomycosis. Gifford[33b] in 1936 was the first to indicate that the nodose lesions of "San Joaquin Valley Fever" or "Desert Fever" were due to coccidioides. Dickson[16] soon after verified the fact that these lesions were manifestations of the primary infection by coccidioides. Dickson and Gifford[17] described the Roentgen-ray findings in this disease and the typical picture includes evidence of enlargement of the hilar glands. Smith[70], an ardent student of coccidioidomycosis, has made a clinical and laboratory study of the cutaneous nodes in this disease. He reported on 432 patients who had the acute disease with erythema nodosum. None of these had acquired coccidioidal granuloma or serious sequelae. Smith considered the nodose eruption a manifestation of a nonspecific allergy in which a coccidioides infection behaved like tuberculosis. Sensitivity to coccidioidin (cf. Beerman and Ingraham[3]) may be established in from 2 to 17 days after onset of symptoms, usually in the second week of the illness. If erythema nodosum develops, it appears shortly thereafter.

In Winer's[89] comprehensive study of the histopathology of the nodose lesions of acute coccidioidomycosis, he concludes that the nodose lesion of this disease is an immunity-producing reaction and indicative of a good prognosis. The histopathologic pattern of the process is characteristic and similar to that of erythema nodosum, regardless of the etiologic factors.

Lymphogranuloma venereum (inguinale). The relationship of this disease to erythema nodosum and to sulfonamides has been indicated above (Simpson[68], Hellerström[39]) showed in 1929 in 2 of 4 cases that erythema nodosum eruptions appeared just when Frei's intracutaneous test was being performed and had attained its maximum. In one case he caused return of the erythema nodosum by renewed injection of the Frei antigen. At this point it is worth indicating that considerable attention has been focused on the relationship of erythema nodosum and the Frei test (Sonck[71]).

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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INDUSTRIAL NOISE: ITS MEDICAL, ECONOMIC, AND SOCIAL ASPECTS

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IN recent years the problem of industrial noise and its effect upon hearing has received increased attention in medical, industrial, legal, and labor publications. In addition to these papers, many meetings were held in 1951 on the noise problem, all of which emphasize the importance of this subject. The industrial noise hazard, however, is not of recent origin. The writer in a previous publication[14] referred to the hearing impairment occurring in braziers and blacksmiths which was known even centuries ago. In the 19th Century reports[2,37,46,13,45], dealing with the professional deafness of boilermakers, railway men, and weavers were published.

In 1937 Bunch[6a] published his extensive monograph on occupational deafness in which he reviewed the previous studies, described the clinical observations, and predicted the medical, legal, and social problems which would arise. During and since World War II, industry expanded, high speed machines were introduced, production increased greatly, and the resultant uncontrolled noise became more intense and more frequent. For the greater part, little attention was paid to excessive noise by either industry or workers; management was too busy with production and employees too concerned with high wages incident to war work. In recent years, important investigations[28,30a,24,15,36] in aircraft, shipbuilding, machine shops, and other industries appeared in the literature. Observations were made amongst workers under actual industrial environmental conditions; certain qualitative and quantitative values were reported. As the result of these numerous investigations, noise deafness assumed greater importance not only because of the hearing loss sustained by some workers, but also by reason of its economic and social implications. No attempt is made by the writer to review the many articles on the effect of noise upon human behavior, health, work efficiency, or work output. These aspects of the noise problem have been previously discussed in the excellent review by Kryter[23] entitled, "The Effects Of Noise On Man."

DEFINITIONS. Noise is defined by the physicist as sound sensation due to acoustic waves occurring at random intensities and frequencies. As found in industry and as used in this paper, noise represents unwanted sound. It is almost constantly present in everyday life. Wells,[48] in describing "The Noises of Civilization and Their Evil Effects", stated that the hearing organ may be affected as the result of noise

exposure in 1 of 3 ways: (1) by suffering loss of function; (2) by developing a state of abnormal sensitiveness; and (3) by acquiring a special tolerance to the noise irritant. It is a fundamental physiologic law that an organ treated to an excess of its proper stimulus must either adapt itself thereto or suffer harm. Wheeler[50a] maintains that in the ear we have an organ which can be impaired by the very stimulus it was presumably designed to respond to. When the normal ear is exposed to noise at damaging noise levels for sufficiently long periods of time, a temporary depression of hearing results, disappearing after minutes or hours of rest. This temporary hearing loss is a physiologic phenomenon and is termed *auditory fatigue*[40]. It is believed to occur in the hair cells of the organ of Corti, and may possibly be associated with chemical changes in the intralabyrinthian fluid of the inner ear. Wheeler[50a,b,c] prefers to call this phenomenon *Temporary Threshold Shift*. The term "overloading of the ear" has also been used. When exposure is longer or intensity greater, or both, a stage is reached where hearing loss increases and recovery is incomplete. The residual hearing loss which no longer returns is called *Noise Deafness or Acoustic Trauma*. Here the damage is permanent and lies in the neutral elements of the auditory apparatus. A second type of damage can occur in acoustic trauma which is characterized by physical destruction of various parts of the sound conduction system; for example, rupture of the ear drums, fracture of ossicles, and hemorrhage. Such injury may result from sudden, very strong auditory stimulation.

Factors Affecting Hearing Loss. As the result of experimental studies in laboratories and investigations in industry, it has been learned that there are many factors which influence the degree of hearing impairment present in noise deafness. The following are some of the more important considerations: 1) intensity and loudness of the noise; 2) frequency spectrum of the noise; 3) period of exposure; 4) individual susceptibility to acoustic trauma; 5) age of subject; 6) co-existing ear disease; 7) character of surroundings in which noise is produced; 8) distance from source; and 9) position of each ear with respect to sound waves.

Intensity Level Of The Noise. It is generally agreed that exposure to intense noise over long periods will result in hearing loss in noise-susceptible individuals. A review of numerous investigations in industry reveals estimates of damaging noise levels ranging between 75 and 115 decibels (db). Bunch[6b] was of the opinion that 80 to 90 db was injurious. McCoy[30a] suggested that practical measures should begin at 100 db level. McLaren and Chaney[28] maintained that the hazardous level was somewhere between 70 and 100 db. On the other hand, Davis[11a] felt that any concern about noise levels under 100 db was unwarranted. According to McCord the intensities of certain sounds as compared to the normal hearing threshold are as stated in Table 1.

The noise levels of various machines encountered in industry at a distance of 3 feet have been reported by Sabine and Wilson[39] as given in Table 2.

McLaren and Chaney[28] made a survey of the general noise level in various departments of an airplane factory and tabulated the sources of noise in the order of their loudness (Table 3).

The most damaging effects upon hearing in our experience are produced by pneumatic hammers, drop forges,

TABLE 1

INTENSITY IN DECIBELS OF CERTAIN SOUNDS AT CERTAIN DISTANCES

Source or Description of Sound	*Average Decibels*
Threshold of painful sounds; limit of ear's endurance	130
Threshold of feeling (varies with frequency)	120
Airplane motor (1,600 revolutions per minute) 18 feet from propeller	115
Steel plate hammered by 4 men, 2 feet	110
Express train passing at high speed	105
Loud automobile horn, 23 feet	100
Pneumatic drill, 10 feet	90
Very heavy street traffic along elevated line	85
Street car crossing tracks	80
Police whistle, 15 feet	80
Very loud radio music in the home	80
Heavy street traffic	75
Snow scraping and shoveling, 15 feet	75
Interior of street car	70
Loud peal of thunder (1 to 3 miles)	70
Usual loudness of radio music in the home	65
Ordinary conversation, 3 feet	60
Speech in a small auditorium	55
Conversational voice, 12 feet	50
Speech in a large auditorium	45
Near outlet of ventilating duct in high school auditorium ("very noisy")	45
Center of New York, quietest time of night	40
Loud fan noise in theater	35
Soft radio music in the home	35
Ticking of watch, 3 feet	30
Quiet street; no traffic	30
Whisper, 4 feet	20
Quiet fan noise in theater	15
Rustle of leaves in gentle breeze	10
Near outlet of ventilating duct in talking picture studio (Planned control of noise)	8
Threshold of hearing; faintest audible sound	0

TABLE 2

INTENSITY, IN DECIBLES, OF CERTAIN MACHINE NOISES AT 3-FOOT DISTANCE

Machine	*Decibels*
Punch presses, various types	96–103
Headers	101–105
Drop hammers	99–101
Bumping hammers	100
Hydraulic press	130
Automatic riveters	95– 99
Lathes (average)	– 80
Automatic screw machines	93–100
Airplane propeller grinding	100–105
Cotton spinning	84– 87
Looms	94–101
Sewing machines	93– 96
Wood planers	98–110
Wood saw	100
Wire rope, stranding machines	100–104
Ball mill	99

air jets, riveting, and chipping operations.

It is apparent that there is considerable difference in intensity levels of machines and some disagreement as to the exact intensity level at which noise becomes hazardous. Other factors previously referred to must be considered. Kryter[23] held the opinion that a fair, perhaps conservative evaluation of laboratory and industrial studies of stimulation deafness demonstrated that the maximum safe intensity at which no deafening effects occur is in the neighborhood of 85 db. According to Davis[11b], this is the level of very loud speech or a shout at 5 to 6 feet distance. This was only for long periods of exposure. On the other hand, for brief exposure up to an hour the intensities necessary to cause deafness are 100 db and over for critical bands of noise. In the reviewer's experience, noise levels above 90 db expose the workers to acoustic trauma. In this connection Guild[18b] and Fehr[12] also quote a 90-decibel level.

At the recent Inservice Training Course[46a] on the Acoustical Spectrum held at the University of Michigan School of Public Health, February 5-8, 1952, several speakers expressed opinions as to what they considered to be overall hazardous noise levels. Glorig[15a] stated, "In general, we positively know that intensities of 130 decibels or more are damaging in a relatively short time; that in most cases 120 to 130 decibels will produce damage in time; that in many cases 100 to 120 decibels will produce damage in time; that in highly susceptible cases 90 to 100 decibels will produce damage; and that intensities below 90 decibels will produce no damage." Kinney[22b] considered 95 decibels as the traumatizing level. House[22a] felt that levels about 90 decibels were dangerous, but qualified this figure by saying it was subject to the duration of exposure, frequency characteristics of the noise, and individual susceptibility.

As pointed out by Wheeler[50b], "So far as the ear is concerned the damage produced by noise is a simple instance of too much stimulus too often applied. This is unfortunately the only point at which the word simple may be

TABLE 3

INTENSITY, IN DECIBELS, OF CERTAIN NOISES IN AN AIRPLANE FACTORY

Source	*Decibel Range*
Drop Hammer	100–130
Rivet Gun (and Bucker)	102–128
Pin Router	104–116
Circular Saw	100–116
Handforming of Sheet Metal	100–110
Speed Hammer	96–110
Trip Hammer	–110
Punch Press	96–108
Band Saw on Sheet Metal	–106
Air Drill	92–100
High-Cycle Milling Machine	– 96
Public Address System	90– 96
Compressed Air	– 92
Spot Weld, Dimpler	88– 92
Filing	– 88
Hydro-Press	84– 88

used when connected with the noise hazard. Such questions as 'How much is too much?' and 'How often is too often?', find us embarrassed by too little information. Further studies are needed for these determinations."

Frequency Spectrum Of Noise. Perlman[35a] made special investigations of the relation of the frequency of traumatizing sound to the degree and type of resultant deafness. His results reveal that for equal intensities the low frequency sounds (below 2000 cycles per second) are less traumatizing than higher frequency sounds. Grove[17], however, states that other workers believe that sounds of low frequencies but high intensities can produce as much damage to the organ of Corti as those of high frequencies. Parrach[34a] declared that injury could occur from frequencies below 200 cycles per second with proper energy levels. As regards ultrasonic frequencies, as ordinarily transmitted through air, Parrach stated that at present there is no evidence that these constitute a hazard to man. There is however a danger to workers coming in direct contact with machines generating these ultrasonic frequencies.

Most commonly used noise-level meters give average over-all intensity readings, omitting the peaks, but not actually analyzing the frequencies. Consequently the deafening effect of component frequencies remains unknown. As Kryter[23] points out, a more careful analysis of the sound spectrum must be made before its deafening value can be estimated. Rüedi and Fürrer[38a,b] in their studies analyzed various frequency bands as to intensity. Fehr[12] has used the dynamic sound spectograph for noise measurement for different frequencies.

Period Of Exposure. Most cases of industrial hearing loss are the result of exposure to high noise levels over a long period of time. In general, it can be stated that the longer the duration of exposure, the greater the hearing impairment. McCoy[30a,b] observed new apprentice workers with normal hearing in the chipping school with exposure to noise levels of 110 to 130 db. Temporary loss was encountered after seven hours, and recovery for most workers took place the following morning. However, continuation of this type of exposure for 1 month led to a permanent hearing loss. Davis[11c] and his collaborators studied the effects of exposure to pure tones and to synthetic aircraft noise at levels from 110 db for varying lengths of time. Their results indicate that the degree of hearing loss is directly related to the intensity and duration of noise exposure.

Cases are recorded of sudden loss of hearing due to single exposure to explosive sounds of very high intensity. Rüedi and Fürrer[38a] have recently described the hearing impairment which occurred in airport personnel who serviced jet-propelled planes (Vampire.) The workers sustained hearing disorders after a relatively short period of exposure, even despite the use of ear defenders. Sound pressure readings in some areas went up to 138 db.

Individual Susceptibility. Wheeler[50a] concludes that there is a marked individual difference in the ability of workers to withstand noise bombardment. He cites a recent industrial study of 175 persons exposed to very high noise levels. As many as 45% retained normal hearing in some instances after 10 years' exposure. On the other hand, 23% displayed severe bilateral hearing loss after only a few months. Larson[24] found hearing impairment in about 50% of shipyard workers.

Shambaugh[40] states that individual susceptibility to noise damage varies between the two ears of one person and particularly between the ears of different persons. Differences also exist in the rate of recovery from auditory fatigue. Just how fast and over how long a period recovery can take place, remains a disputed question that needs further investigation.

Effect Of Age. Loss of hearing, which is an accompaniment of advanced age, has been given the name presbycusis. This hearing loss in older people is supposedly due to simply atrophy and degeneration of the end organ. Bunch[6a] suggested that it is the cumulative effect of daily noise exposure over the years which is responsible for gradual deterioration. The hearing loss is of the perception type affecting the higher frequencies and rarely involving the lower scale. It is associated with a loss of bone conduction. Studies showing the effect of age upon hearing have been reported by Wolf[52] in 1874, Bezold[5] in 1894, and Grant[16] in 1902. With the introduction of the audiometer several series of studies made by Bunch[6c,d,e] again revealed the increasing loss in high tones in each decade of life. Similar findings were reported by Ciocco[9] in 1932. The more recent reports of The National Health Survey[3] (U.S. Public Health Service), The World's Fair Hearing Tests[42], and The San Diego County Fair Hearing Survey[47] include extensive studies on large numbers of individuals in a random population. A comparison between the hearing losses for the San Diego County Fair (S.D.F.) and the World's Fair (W.F.) population studies is shown in Table 4.

Although knowledge of the normal aging process of the human ear is still incomplete, the San Diego and World's Fair studies represent the best available information at present. They permit study of the hearing loss in workers with normal variation due to the age factor.

TABLE 4

	Frequency:	440		880		1760		3520		7040	
Age	Fair	Sex M	F	M	F	M	F	M	F	M	F
10-19	S.D.F.*	−0.3	0.2	−1.0	−0.1	−1.9	−0.1	−3.2	−4.1	−3.3	−5.3
	W.F.**	1.0	0.5	0.3	0.2	−0.3	−1.1	−1.2	−4.4	−0.4	−3.6
20-29	S.D.F.	−1.3	−1.3	−0.7	0.7	0.4	−0.4	3.8	−3.8	3.9	−3.9
	W.F.	0.0	0.0	−0.2	0.2	−0.1	0.1	2.0	−2.0	1.5	−1.5
30-39	S.D.F.	0.3	3.6	1.3	3.1	2.2	2.7	7.7	−0.7	6.5	−0.1
	W.F.	1.4	2.6	1.3	2.6	2.3	2.9	8.2	2.4	7.7	4.8
40-49	S.D.F.	1.3	5.3	2.4	4.3	6.0	5.2	13.2	0.7	13.3	3.6
	W.F.	3.7	6.0	4.5	5.8	7.0	6.7	17.7	7.8	16.8	11.9
50-59	S.D.F.	4.2	6.9	4.9	7.3	11.9	10.4	25.0	7.3	27.9	12.2
	W.F.	6.8	10.3	7.7	9.8	12.1	11.0	25.6	13.8	24.0	19.7

* San Diego County Fair.
** World's Fair.

Co-Existing Ear Disease. Ears with a pre-existing conduction lesion are less susceptible to noise damage than ears with normal hearing. This is explained on the basis that an existing conduction lesion will protect the ear, just as does an ear plug or defender, and accordingly reduce the intensity of sound reaching the inner ear. McLaren and Chaney[28] felt that these individuals with conductive lesions

need not be excluded from noisy areas. In Fox's opinion individuals with an existing nerve type hearing loss should be cautious in subjecting themselves to extremely noisy intensities. This is particularly true of young individuals.

Character Of Surroundings. The environment in which the worker is exposed to noise naturally assumes importance. Room acoustics play an important part. Sounding boards, reverberating chambers, deflecting walls, and other things enchance prevailing noise and aggravate damage. This is a problem of interest to acoustical and safety engineers.

Distance From Source. The distance from the sound source is of importance, as shown in the inverse-square law of relation of sound intensity to distance. This law, however, applies only to wind-free open spaces. Room acoustic conditions, as commonly found in industry, alter the law.

Position Of Ear To Sound Waves. While this is of particular importance to military personnel exposed to explosions, gunfire, and mortar shell, the ears of the industrial worker subjected to incessant clicks and explosive sounds will suffer the greater loss.

Characteristics Of Hearing Loss. Perlman[35a] writes, "The early cases of acoustic fatigue and/or noise deafness are characterized by a sharply localized dip in the threshold curve between 4,000 and 6,000 cycles per second. At this stage the subject may experience no difficulty in hearing. As trauma continues, the hearing for the still higher frequencies is affected, but again very little noticeable effect will occur to the subject. Then the hearing for sounds below 4,000 cycles per second becomes affected and with this loss difficulty in understanding some speech sounds (consonants and whispered voice) are noted." Grove's[17a] experiences are similar to those of Perlman. He emphasizes that development of noise deafness is slow and insidious, and that the worker is apt to disregard it or be unaware of its existence until he is quite deaf.

The writer of this review has often observed that tinnitus is one of the common and earliest symptoms. The Temporary Threshold Shift phenomenon has been demonstrated by McCoy[30a] in an investigation involving 100 men with normal hearing. After working for 7 hours at an exposure intensity of 110 to 130 db, a considerable number of men had symptoms of temporary hearing loss associated with tinnitus and ear discomfort. After an exposure of 1 month's duration a "representative group" of these workers had permanent hearing loss.

Structural Changes. In a previous article, Fox[14], reviewed histologic and postmortem studies.

"To Habermann[19] goes credit for the first report of the pathologic changes in the inner ear in acoustic trauma. His report concerned the findings in a 75-year-old coppermill worker. He was able to demonstrate damage to the organ of Corti and the spiral ganglion. Although the histology of several human temporal bones has been reported by Wolff[53], Guild[18], and others, the material has not been illuminating, and our knowledge of the pathologic changes of the inner ear comes mainly from experimental studies. These date back to 1907, when Wittmaack[35b] studied the problem by blowing a shrill whistle into a glass funnel placed in a guinea pig's ear. Since then, many successful methods have been used to produce stimulation deafness; to cite a few, Yoshida[35b] used a pneumomassage machine on a guinea pig's ear; Lurie and associates[27], Wever and Smith[49], and Rüedi and Fürrer[38b] delivered pure tones into the animal's ear; and Hoessle[22], Guild[18a], and Perlman[35c] each used pistols near the animal's ear. In recent studies Lindquist[25] has correlated the hearing loss with histologic changes in the inner ears of cats subjected to pistol shots.

These experiments and others have shown that the injury is most severe in the middle region of the cochlear duct, that is, the upper part of the basal coil in human beings and most animals. Mild injury consists of disruption or degeneration of the outer hair cells and their supporting cells in the upper basal coil, with secondary degeneration of ganglion cells and nerve fibers supplying that area. Severe injuries are more widespread and cause more extensive damage to the end organ, such as degeneration of both outer and inner hair cells, flattening of the organ of Corti, or complete loss of the organ of Corti.

Past experimental studies have failed to explain why the upper basal coil which analyzes the 4000 cycle-per-second frequency range is more vulnerable to stimulation injury. Popular theories are as follows: 1) that the structures of the upper basal coil are more fragile; 2) that the selectivity is due to a physical property of the stimulus; 3) that the blood supply is less favorable in this region.

It is apparent, then, that either sustained or short-lasting sound stimuli of sufficient amplitude may cause damage to the end organ of hearing. It is probable that there is such a violent displacement of the basilar membrane and attached organ of Corti that both reversible and irreversible cellular injuries occur."

Kryter[23] points out that although hearing loss around 4000 cycles per second is found in industrial workers, it is also frequently found in so-called normal populations without ear infection. He suggests that the cause, rather than being a structural weakness of the blood supply or a particular region of the cochlea, is the result of auditory acuity and spectrum of sound stimulation. He cites the work of Davis who reported hearing loss about one-half octave above the frequency of tonal stimulation, and that of Perlman who found the greatest loss one octave above the stimulus tones. Rüedi and Fürrer[38b] also found the maximum loss one octave higher than the pure tone stimulus. Kryter[23] concludes that since the ear is most sensitive at about 2000 cycles per second, one would expect that with exposure to intense noise containing all frequencies at about equal intensities, the greatest hearing loss would be in the region between 2000 and 4000 cycles per second.

MEDICOLEGAL CONSIDERATIONS. Grove[17a,b] states that loss of hearing, the result of industrial noise exposure, is a compensable occupational disease in 33 states in addition to the District of Columbia, Hawaii, and Puerto Rico. He issued words of warning and advice to management, workers, industrial physicians, and others involved as to the medicolegal implications. On behalf of the Subcommittee on Industrial Noise of the American Academy of Ophthalmology and Otolaryngology, he outlined a program for industrial investigations and preventative measures. Nash[33a] in 1947 revealed that in one industrial shop, management was confronted with 300 to 350 hearing loss claims involving one and one-half million dollars. Other authors[17a,6a] have referred to management's desire not to stir the "sleeping dog", because of the fear of claim. During 1951, the "sleeping dog" has been aroused, and a large number of claims for hearing loss due to industrial noise exposure are now in law courts throughout the country, especially in New York[33a], New Jersey[32a], California, and Wisconsin[32b]. Undoubtedly many similar claims have been introduced in other communities. Commenting on the deluge of claims that have arisen, Yaffe[54] declares that "industry is becoming aware that while it may not yet have to control noise, it will have to pay for the injury resulting as a consequence."

Symons[44] raises the following medicolegal question "How and when can it be determined that the employee's hearing loss is permanent, so as to entitle him to an award?" He attempts to answer this question by referring to

a letter[44] from Dr. H. House stating that the committee on the conservation of hearing of the American Academy of Ophthalmology and Otolaryngology had adopted the following statement of policy as formulated by its Subcommittee on Noise in Industry. "Hearing loss produced by prolonged exposure to loud noise may be considered as permanent 6 months following complete removal of the individual from the area of loud noise." Nash[33b], relating his experience with a large number of claimants for alleged industrial hearing loss, stated that at least 50% of the workers after removal from noisy environment showed improvement in hearing. He observed that this improvement may be extended over a 6 to 18-month period in some cases.

In a discussion of the proper method for determining the percentage of the hearing loss due to occupation, Symons refers to possible contributing factors, such as toxic, metabolic disturbances, infections and ear diseases, as well as to normal loss due to age. He goes into considerable detail regarding the relative merits of the American Medical Association (A.M.A.) method and the so called "Point 8" method for determining the percentage loss of hearing for speech. In 1942, Carter, secretary of the Council on Physical Therapy for the A.M.A., wrote an excellent review[8] of the methods used for estimating percentage loss of hearing. He proposed that the method to be used only in medicolegal or industrial cases should be: 1) easily understood; 2) easily and quickly applied; 3) free of complicated mathematical calculations; 4) easily interpreted before any jury; 5) designed for both ears jointly considered as a single hearing component; 6) based on air conduction data obtained from standard audiometers; 7) weighted to give preference to the frequency range of the spoken voice; 8) founded on the best available acoustical and clinical scientific evidence." Carter then reviewed 11 methods which had been used in the past including the 0.8 (Fletcher) method. He concluded that the Sabine method which was a weighted chart and the basis for the present A.M.A. hearing loss chart[10a] came nearer to meeting the requirements as proposed in his paper than any of the methods.

In evaluating hearing loss claims resulting from noise exposure, it has been the policy of the writer (M.S.F.) of this review to determine the loss based upon the A.M.A. hearing chart of 1947 (Table 5). If the worker is older than 29 years we subtract from the determined percentage loss, that amount which normally could be expected due to the age factor.

Symons requests the medical profession to engage in the necessary examinations and studies so as to formulate definite standards with respect to the etiology and evaluation of noise deafness. Sterner[43], however, raised the question as to whether or not this is the proper time for establishing standards.

Davis[11d,b] and Symons[44] refer to the desirability of testing subjects for their ability to hear speech (speech audiometry) at controlled intensity levels. The individual's ability to understand speech at 3 different levels is used to express the hearing function as the social adequacy index. It seems, however, that under present conditions and with the equipment available, the audiometer is still the best means for determining the hearing status of workers.

On the basis of the foregoing, it is apparent that there is considerable dispute regarding quantitative values and standards. The Council on Physi-

cal Medicine[10b] of the A.M.A., in conjunction with acoustic and otologic representatives, at a meeting in April, 1951, emphasized the need for measuring environmental noise levels with special reference to various bands in the sound spectrum. In this connection McGrath[31] recently proposed a classification of industrial noise areas based upon the intensity level of noise and the distribution of the sound spectrum.

TABLE 5

REPORT OF COUNCIL ON PHYSICAL MEDICINE
METHOD OF CALCULATING HEARING LOSS (Percentage)
J. Am. Med. Assn. February 8, 1947

db	512	1024	2048	4096	Total
0					
5					
10	.2	.3	4.	.1	1.0
15	.5	.9	1.3	.3	3.0
20	1.1	2.1	2.9	.9	7.0
25	1.8	3.6	4.9	1.7	12.0
30	2.6	5.4	7.3	2.7	18.0
35	3.7	7.7	9.8	3.8	25.0
40	4.9	10.2	12.9	5.0	33.0
45	6.3	13.0	17.3	6.4	43
50	7.9	15.7	22.4	8.0	54
55	9.6	19.0	25.7	9.7	64
60	11.3	21.5	28.0	11.2	73
65	12.8	23	30.2	12.5	79
70	13.8	25	32.2	13.5	84.5
75	14.2	27.2	34.0	14.2	89.6
80	14.8	28.8	35.8	14.6	94
85	14.9	29.8	37.5	14.8	97
90	15.0	29.9	39.2	14.9	99
95	15.1	30.0	40.0	15.0	100

Formula for bilateral hearing loss: Add loss in each ear at 4 frequencies given above. Multiply loss in better ear by 7. Add loss in worse ear. Divide total by 8.

than now exists for the determination of degrees of hearing loss. The council was specific that the diagnosis of occupational deafness must be dependent upon a pre-employment audiograph record.

MANAGEMENT OF NOISE DEAFNESS. On the basis of the structural changes which take place in noise deafness, it is apparent that there is no medical or surgical treatment that can successfully restore hearing loss. The damage to the hair cells and neural elements is permanent and irreversible. The problem must, therefore, be approached from a preventive standpoint. A prime objective is to conserve the hearing of workers and others exposed to loud noise. To achieve this purpose, the cooperation of all groups involved in the problem is required. This includes workers, industrial management,

He asserted that the results would conform more closely to scientific findings and enable investigators to differentiate harmful environments from those which are not detrimental. The Council on Physical Medicine[10b] of the A.M.A. also recommended the establishment of audiometric testing programs as part of the pre-placement medical examinations of workers; and suggested devising a better method

industrial physicians, safety engineers, union officials, and others. During 1951, the writer (M.S.F.) of this review examined a large number of Wisconsin workers who had filed claims for hearing loss attributed to their occupations. The absence of adequate pre-employment ear and audiometric studies, noise exposure readings, and other important information made evaluation of these cases difficult. In Fox's opinion, the problem cannot be solved by lawyers, legal bodies (industrial commissions and courts), or the personal desires of workers, insurance carriers, or management. The relationship of noise deafness to workers will have to be investigated and studied where noise exists. Several phases of investigation and control of industrial noise have been suggested:

1) The gathering of statistical data should include surveys of noisy areas in industry plus pre-placement audiometric and otologic studies of workers. Follow-up audiometric examinations should be performed as indicated on workers exposed to hazardous noise levels. The instrumentation and techniques for measurement and evaluation of industrial noise have been discussed by Beranek[4], Callaway[7], and Fehr[12].

2) The development and setting up of quantitative standards for evaluating the problem.

3) Investigation of pre-employment selectivity tests to discover noise-susceptible individuals. Such tests have been proposed by Wheeler[50c] and Wilson[51]. These tests are explained by Guild[18b] as being based on the general principle of fatiguing ears to a loud sound of known intensity for a short time, and then measuring the rate of recovery to the original threshold of hearing. The assumption is made that the ears which recovered most slowly from the effects of the standard experimental sound would be the ones most vulnerable to permanent injury by more severe or more prolonged exposure to sound. Guild[18b] believes that these tests are of sufficient practical importance so that large scale follow-up studies should be made to find out whether ears that recover slowly in fatigue tests actually are the ones that suffer the most hearing loss in noisy industrial situation.

4) The development of methods and treatment which make possible elimination or reduction of the noise entering the ear. These objectives may be achieved by the following methods: a) The planning of machinery and tool re-design to eliminate noise at its source; b) The substitution of processes in industry in place of noisy operation; c) The rotation of working personnel; and d) The use of ear plugs and ear defenders to lessen the deleterious effects of noise.

a) The planning and re-design of machinery is a problem for safety and acoustic engineers. While this approach to eliminate or lessen damaging noise is very important and most desirable, practical achievement is not always possible, as evidenced in the drop-forge and jet-plane industries. Hardy[20] points out that most noisy conditions which exist today are the result of comparatively modern machines. The emphasis in modern design has been to get more horsepower per pound and let the decibels fall where they may. However, with good design many noise reduction jobs have been performed. Fehr[12] also cites methods for the reduction of industrial machine noise.

b) The substitution of other industrial processes for noisy operations has been used in some instances. Nash[38a] relates the consideration given to using

a welding process in place of the usual riveting and drop hammer method of construction of steel freight cars. He claims that such a change in method of construction would reduce the life expectancy of a freight car from 11 to 4½ years, and lessen the stability of the product. The architectural and technical aspects of industrial and office quieting have been illustrated in the papers of Ashley[1], Harris[21], London[26], and Smith[41].

c) The rotation of working personnel would allow for shorter periods of exposure and longer recovery periods. This, however, is an impractical suggestion and would meet with objections from workers and management.

d) If hazardous noise cannot be eliminated or reduced, then one can resort to the use of ear plugs or defenders which will lessen intensity of the noise as it passes through the ear canal. Kryter[23] points out that 2 main varieties have been developed and used, the plug type that fits snugly into the external meatus of the ear, and a cushion type held by a head band or in a helmet that lies around and over the ear. Among plugs, there are many varieties: dry cotton and wool, wet or wax-impregnated cotton or wool, wax, plastic and rubber. Wheeler[50a,d] investigated many of the commonly used ear plugs and muffs. He concludes that suitable ear defenders should be comfortable, effectively attenuate the noise, and have a low replacement cost. The ear plugs should be comfortable to the wearer, and made of materials which will not act as an irritant to the ear canal. The problem of contamination and infection must also be considered. Some employees have been reluctant to wear ear plugs, in the belief that it is an expression of weakness. Another objection has been that the plugs would interfere with speech and ability of the workers to hear signals and orders. In this respect Kryter[23] states that where the noises produce effective masking of more than 60 db, the wearing of the ear plugs actually improves the reception of speech. This view, however, is not shared by other writers, who believe that with effective attenuation of the noise, ability to hear speech is simultaneously reduced. While in extremely noisy operations maximum attenuation is desired, Wheeler[50a] in his studies found that with most present commercial devices reduction of about 35 db was the most that could be obtained even under ideal conditions.

Industry has shown a willingness to adopt, as a safety measure, the use of ear defenders where noise could not otherwise be abated. Investigations now in progress give hope for the development of ear protection which will fulfill the requirements as outlined by Wheeler.

Conclusion. The writer of this review has attempted to show that occupational hearing loss is an old problem which has become aggravated with the introduction of modern machinery generating high noise levels. Many laboratory studies, particularly in animals, have been made, regarding stimulation deafness. During the past decade several studies have been made among workers in industry. Despite the attested value of these studies, numerous quantitative data and functional relationships require clarification. Many employers have been unaware of the noise problem, either because of lack of information or because of not having been confronted by hearing loss claims. The noise problem has an economic as well as a humanitarian aspect. Noise deafness itself cannot be successfully

treated. If the traumatic noise hazard is properly investigated where it exists, measures will be found to control and prevent hearing loss. Such a program will require the cooperative efforts of all involved. The experience of industry and labor in dealing with other occupational hazards (lead and dust) offers hope for the successful solution of the problem of industrial noise.

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PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 15, 1952

Factors Regulating Capillary Blood (P^{32}) Volume in the Lungs. DOMINGO M. AVIADO, JR., M. D., PETER H. BULLE, M. D., A. H. NIDEN, and CARL F. SCHMIDT, M. D. (Department of Pharmacology, School of Medicine, University of Pennsylvania). The control of the pulmonary circulation was investigated in dogs (morphine and chloralose anesthesia) with closed chest by continuous measurements of: (a) pulmonary flow by the standard direct Fick method; (b) pressure of the cannulated lobar artery; and (c) lung blood volume. Following the earlier work of Nylin (Am. Heart J., **34**, 174, 1947) and Reid (Ann. Surg., **132**, 327, 1950), the relative amounts of erythrocytes tagged with phosphorus^{32} in the lung capillaries were estimated by a beta counter applied close to the surface of the lung. About half of the measured radioactivity was due to pulmonary flow. The other half was from the stagnant blood remaining after flow was temporarily obstructed by inflation of a balloon in the pulmonary artery. At least three procedures demonstrated the factors regulating pulmonary capillary blood volume (PCB).

(a) Bleeding maintained the PCB at a constant level and decreased pulmonary flow and pulmonary arterial pressure. There was a shifting of blood from the peripheral circulation to the stagnant component of PCB. This adjustment was not seen after vagotomy and during a rapid massive hemorrhage.

(b) Blood infusion caused augmented PCB and pulmonary arterial pressure by pulmonary venous constriction. This temporary storing of blood in the lung capillaries was not dependent on vagal innervation. A similar mechanism could be elicited by steam inhalation and alloxan edema.

(c) Anoxia caused higher levels of PCB and pulmonary arterial pressure mainly by increasing pulmonary flow. Reduction of oxygen content of ventilating air or of perfusing blood elicited dilatation of perfused vessels of an isolated lung. This dilatation was partly responsible for the observed increase of PCB in anoxic intact dogs. The constriction effect on pulmonary vessels of anoxia as reported by others (reviewed by Nisell, Acta Physiol. Scandinav., Suppl. 73, 1950) was not confirmed.

The following procedures did not significantly change PCB: intravenous injections of epinephrine and sodium cyanide, electrical stimulation of peripheral and central vagus, and of carotid sinus nerves, and clamping of carotid arteries.

Skin Oxygen Tension (by Polarography) vs. Arterial Oxygen Saturation (by Oximetry); Time Lag for Oxygen to Travel from Blood to Skin. R. PENNEYS, M.D., and H. MONTGOMERY, M.D. (Periph. Vasc. Sect., Robinette Fdtn., Hosp. Univ. Penna.) Oxygen was inhaled and the first change in arterial saturation (ear) and in O_2 tension of skin of an extremity were noted. Changes in blood flow in the extremity influenced the time of change of ten-

sion but had no influence on the time of change of saturation. In warm skin, with rapid circulation, oxygen inhalation caused a change in oxygen tension 18 seconds after the saturation change. In cool skin, with reduced circulation, the change in tension was delayed by at least an additional 60 seconds. When the circulation to the skin was subsequently increased reflexly by the application of heat to the body, the lag in tension change reverted to 18 seconds. In hot skin, with extremely rapid blood flow brought on by the direct application of heat, the tension change occurred almost simultaneously with the saturation change. These experiments show that the tension lag varies inversely with the rate of blood flow through small blood vessels. This is confirmed by experiments in which the circulation to the warm skin was re-established after arterial compression. In such skin, the change in tension lagged behind the first pinkness of skin to the same extent that it lagged behind the saturation change. The lag of the first change in the skin tension behind that of the arterial blood was the same whether pure O_2 or 10% O_2 was inhaled.

Preliminary Observations on the Oxygen Tension of Normal and Abnormal Skin. FREDERICK URBACH, M.D. (Damon Runyon Clinical Cancer Research Fellow, Department of Dermatology, University of Pennsylvania) and GEORGE PEIRCE. The oxygen tension of normal and diseased human skin was measured *in vivo* with the open type platinum oxygen cathode. pO_2 was recorded when electrode current had become stable. All studies were performed in a warm room and with good vaso-dilatation. The pO_2 of identical normal skin areas showed marked individual and daily variations. These variations were probably due to differences in cutaneous vascularity and blood flow. However, consecutive measurements of pO_2 in any one area under identical conditions of temperature and blood flow varied no more than 20%. The pO_2 of all malignant tumors examined (basal cell epithelioma, squamous cell epithelioma and cutaneous lymphoma) was less than 10% of the mean of adjacent normal skin. Intracutaneous cellular nevi, cutaneous sarcoidosis, xanthoma nodules, psoriasis and lichen planus had a pO_2 as low as that of malignant tumors. Oxygen tension of cutaneous myxedema, scars and stasis ulcers was lower than normal but not as low as that of the above mentioned groups. There was no significant difference in pO_2 between the adjacent normal areas and senile and arsenical keratoses, premycosis fungoides, and atopic and seborrheic dermatitis. Small doses of roentgen-ray (300 r) had no effect on cutaneous PO_2. At the height of the radiation reaction large doses of roentgen-ray (4200 r) depressed pO_2 to tumor levels. This effect is thought to be due to the occlusive vasculitis produced by radiation. After subsidence of reaction the PO_2 returned to normal. The reduction of pO_2 observed in cutaneous disease parallels the extent of infiltration of the skin with neoplastic, granulomatous or inflammatory cells. This reduction of pO_2 may be caused either by increase in cutaneous metabolism due to a great increase in cellularity associated with the disease state investigated, or possibly to differences in capillary-electrode distances.

An Inhibitor of Brain Hexokinase Present in Blood Plasma. M. ZACCO, M. D., (U.S. Government Fellow from the University of Bari, Italy.) and M. G. SEVAG, PHD. (Department of Microbiology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.) In a previous preliminary report (Zacco, M. Boll. Soc. ital. biol. sper. **27:** 326,

1951.) it was shown that fresh tubercular blood plasma inhibits the activity of brain hexokinase. Normal plasma *per se* shows no inhibitory action.

A water extract of the acetone powder of homogenized rat brains was used as a solution of hexokinase, the activity of which was determined by measuring the decrease in the amount of glucose in the reaction system.

About 83% of the freshly collected tubercular plasma inhibited the activity of hexokinase from 25 to 80%. Under identical conditions only about 14% of all the normal whole plasma specimens exercised inhibition. The inhibitor in tubercular plasma is inactivated on standing for 12 hours even in the refrigerator. However, both the inactive tubercular and normal plasma manifest the inhibitory property on dialysis against distilled water. This activation fails to occur when plasma is dialyzed against physiological saline. This finding could indicate that under normal conditions the inhibitor exists in a non-dissociable complex form, and on dialysis it dissociates and manifests its inhibitory property.

On prolonged dialysis apparently all of the inhibitory property is found free in solution. At this stage it is stable for several weeks and is resistant to heating for 1 hour at 55°C. It is not sedimentable even by a centrifugal force of 300,000 g. It is not counteracted by insulin.

Attempts to isolate the inhibitor have yielded a partially purified product. Due to the sparsity of the isolated material we have not been able to accomplish the purification and identification in a satisfactory manner. However, stated conservatively, our preparations represent a concentration of about 100 fold. One milligram of this material in the reaction system exercises from 60 to 73% inhibition. It is inactivated, when incubated for 10 hours, with fresh but not with dialyzed plasma.

On acid hydrolysis of 1 mg. of material, it gives a strong ninhydrin test which would indicate a protein content of about 25%. Total nitrogen values range from 30 to 50 micrograms nitrogen/mg. of material. On acid hydrolysis reducing substances such as glucose range from 10 to 80 micrograms/mg. of material. Tabulation of the respective data fails, however, to indicate a relationship between nitrogen or reducing values and the inhibitory activity of the various preparations.

Results may seem to indicate that the most active materials obtained, contain ca. from 0.07 to 0.5 microgram of Zn^{++}/mg. determined by the dithizone reagent. Zn^{++}/*per se* fails to exercise any degree of inhibition at a concentration of up to 10 micrograms/system. Whether the active material is a zinc-containing substance, is yet to be determined.

BOOK REVIEWS AND NOTICES

PEPTIC ULCER: CLINICAL ASPECTS, DIAGNOSIS, MANAGEMENT. Edited by DAVID J. SANDWEISS, M.D., F.A.C.P., Assoc. Attend. Physic., Div. of Int. Med., Harper Hosp., Detroit, Mich. Pp. 790; 164 ills. Phila.: W. B. Saunders Co., 1951. Price, $15.00.

THE etiology of peptic ulcer has defied isolation since Cruveilhier's time (1835). The literature on the subject has been most voluminous as well as confusing. This volume, by utilizing the experience of some 70 different specialists working in various aspects of the problem, accomplishes a crystallization of facts. This not only separates the wheat from the chaff, but also elevates the known pathophysiology of peptic ulcer above the handed-down folk-lore. Yet, as one finishes this easily readable book, one is made aware that the work to explain this disease further must continue.

The practical aspects of management of almost every conceivable situation that might develop in peptic ulcer are discussed thoroughly. The relationship of the General Adaptation Syndrome to peptic ulcer makes a most interesting chapter.

We express our thanks and admiration to Dr. Sandweiss and his committee of the American Gastroenterological Association for this worthy and unique volume. S. B.

MEDICAL BOTANY. BY ALEXANDER NELSON, Ph.D., D.Sc., F.R.S.E.; reader in botany and lecturer to medical students in University of Edinburgh. Pp. 354; ills. Edinburgh: E. and S. Livingstone, Ltd.; Baltimore, Williams & Wilkins Co., 1951. Price, $6.50.

"MEDICAL BOTANY" is a useful, although not outstanding, book. It contains considerable botanical information which is not unnecessarily technical and it does not obscure the other valuable information. The few illustrations are good.

The first section covering more than half of the book is devoted to a description of foodstuffs with special emphasis on their composition. The second section lists and describes most of the known drugs of plant origin. Many of these descriptions are too brief and too much emphasis is placed on a large number of drugs no longer considered important in American medicine. The third section considers, in a superficial manner, plants which cause disease. This section also includes a chapter on the identification of plants.

The title, "Medical Botany," does not seem to describe adequately the contents of this book. F. E.

ATLAS DER PATHOLOGISCHEN ANATOMIE. By ROBERT RÖSSLE, Dr. Med., formerly Director Pathologic Inst., Univ. of Berlin, and KURT APITZ, Prof. and Prosector, Charity Hosp. Pp. 298; 564 ills., mostly in 4 colors. Stuttgart, Germany: Georg Thieme-Verlag, 1951. Price, DM 87.00 (about $20.70).

THIS is an atlas of gross morbid anatomy somewhat less than half of which is devoted to text and the remainder to 564 illustrations, almost all of which are in color. The plates are reproductions of photographs. Here at last is an atlas depicting the gross morphologic changes in most of the principal diseases. The text is concise, the arrangement is sensible and convenient. The photography and color reproduction are superb, better than any American work with which I am familiar. The authors have chosen the classical lesions of the more common conditions and avoided material which is so often included for the sake only of increasing the total. The illustrations are so faithful that one needs little knowledge of German to appreciate this atlas, but they are so excellent and so informative that the text deserves translation for the American market. E. A.

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1. UGO BENZI. MEDIEVAL PHILOSOPHER AND PHYSICIAN. 1376–1439. BY DEAN LOCKWOOD. Pp. 441; no ills. Chicago: Univ. of Chicago Press, 1951. Price, $8.00.
2. PARACELSUS. MAGIC INTO SCIENCE. BY HENRY M. PACHTER. Pp. 360; 12 ills. The Life of Science Library. New York: Henry Schuman, 1951. Price, $4.00.

THESE two books may profitably be considered together—the *Ugo Benzi* illustrating the peak of late ("high") medieval philosophic and clinical medicine; *Paracelsus*, who lived one hundred years later, typifying, as no one could better, the brilliant yet baffling, many sided and often incomprehensible, genius of the Renaissance.

In *Ugo Benzi*, Dean Lockwood, author and professor emeritus at Haverford, presents the more scholarly and more complete study, granted that his subject lends itself more readily to both these qualities. Brought accidentally in contact with a forgotten manu-

script in the Antonelli collection at Ferrara while hunting in it for a play of Aristophanes, Lockwood found—"a perfect example of serendipity"—that the manuscript collection also contained a unique and unknown Vita of Ugo. This had been written shortly after his death by his son, Socino, and was "probably the earliest independent and authentic life of a physician in existence." Thus began a search for early source material about Benzi that led over 20 years through many great libraries to culminate in what will undoubtedly long remain the definitive presentation of Benzi's life and works.

Ugo's life fell in a period when the dry scholasticism of the Middle Ages was changing—at considerably different times to be sure in different lines of human endeavor—into the exuberant, often boisterous, colorful period of the Renaissance. The author points out how the sources until recently available on Benzi—biographical sketches, local studies, anecdotes and so on—were in most cases unavoidably fragmentary and even erroneous. However, in recent years, not only Socino's "Life" but also the voluminous publications of the archives of ancient universities and similar source materials have radically widened the opportunities for scholars who like Lockwood can devote two decades or more to pursuit of a single theme. From this study there emerges a clear picture of a leading humanist-physician of 6 centuries ago, his physical appearance, a surprisingly full chronology of his 63 years, and a careful analysis of his professional output. Following brief notice of 3 "premedical" philosophical essays, the author considers Benzi's 5 great Commentaries (on the Tegni of Galen, the Aphorisms of Hippocrates and 3 of the Fens of Avicenna's Canon), 9 independent Quaestiones, 106 Consilia, and the Trattato—a *regimen sanitatis* in the vernacular. These except for the absent ninth book of Rhazes *ad Almansorem* thus constitute "a complete university course in the theory of medicine as taught in the schools of that period. A full generation after Ugo's death these works began to be published in printed form in a *Corpus*, which was republished in varying forms by different editors and printers. All these details are minutely dissected in one of Lockwood's 15 appendices, which, in passing, occupy considerably more space than the text of the biography proper.

The work is valuable, too, in the light it throws on the state of medical theory and practice in the transition period of the 15th century. From this aspect, Ugo's Consilia (which are given here in toto in Latin, with translations of the most important) are of special interest as practically the only kind of clinical writings of the period. Yet even here, the meager personal observations and the hopelessly inadequate directions for treatment precribed are not infrequently mingled with theoretical disquisitions, that are quite irrelevant to the case in question. The learned doctor could not long remain the simple practitioner!

The author has been remarkably successful not only in bringing before us "the living figure of Ugo in his true environment" but also in producing a good picture of "the physician's relation to society and of the layman's attitude to the physician and to medicine."

The style of the book while necessarily dry for the most part is always scholarly and easy to understand, and furthermore is now and then pleasantly enlivened with such phrases as "no putterer or dabster," "the scrappiest of scrapbooks." If the connecting thread of the items of Ugo's life and productions is found at times difficult to follow, this can properly be ascribed to the wealth of detail by which each one is accompanied.

Turning to Pachter's book on Paracelsus, a very different situation presents itself. The author, "a cultural historian" who apparently is neither physician nor scientist, quite understandingly is chiefly interested in Paracelsus' life as a "clue to the riddle of the Renaissance." For medical readers he dwells overmuch on such aspects as Paracelsus' identification with the legendary Dr. Faustus (involving the philosophy of man), his role as a Magus (the "Magic Into Science" of the sub-title), and as a "partisan of a lost cause . . . left politically homeless" in the struggle between the Papacy and the Reformation.

The picture of this master of inconsistency, with his life of many heights and chasms and his unusually varied activities has been obscured for posterity by his tendency to coin strange words and to make his writings difficult for his enemies and would-be imitators to understand. The flow of the narrative is further interrupted by an awkward style, a fault easily pardonable to one not writing in his native tongue and perhaps unfamiliar with the many intricacies of the English vocabulary. More serious is the distortion which makes Aschner assert that certain of his "cures are based on Paracelsus' description of 'tartar'." One notes, too, that in Hippocrates' first aphorism, for *experimentum* (πειρα) which we translate as experience, the author has preferred "experiment," which

today has a very distinct and different meaning.

Accepting these shortcomings, none of which are fundamental, we find that a vigorous and rather novel picture has emerged—Paracelsus' triumphs and failures, his theories of disease and its treatment, many fantastic but many practically successful and far in advance of his times. Whether or not he is entitled to be called the founder of biochemistry and chemotherapy and even of experimental science, and the foreshadower of modern psychiatry—and here Dr. Pachter is cautious in drawing conclusions—Paracelsus certainly was far from the mere quack and wine bibber that he has often been called and was undoubtedly a potent influence in freeing human thought from the deadening weight of ancient authority. But this antagonism was when he thought the authority was deadening and not because of its age. He burned the works of Galen and Avicenna, but was a follower of Hippocrates and a believer in the healing forces of nature. Necessarily limited by the paucity of scientific knowledge of his times, he earnestly sought for the truth and the reasons for things, pursuing basic problems still unsolved, so that his figure remains more alive today than do those of many leaders of the science of later days.

With the surer touch that one might expect from a cultural historian, Dr. Pachter portrays the most interesting part of this amazing life: its last 10 years, including his descent into the pit of failure, his transformation from an arrogant materialistic philosopher to a contrite preacher who attributes all healing to God, the Soul of the World who is above Nature. A wandering preacher who subsisted by begging, he helped halt the plague at the little town of Sterzing but was soon driven out. Coming to the mines in the Inn valley he found the material for "On Miner's Consumption," the first book written (1534) on an occupational disease. In 1536 came his "Great Surgery Book," his only major work printed (1536) in his lifetime, in which this skillful surgeon emphasized how to avoid operations. "The surgeon should know that not he but Nature is the healer." And the same year gave birth to his "Philosophia Sagax," "the most confused book in the German language, it also has been pronounced the most profound." Still to be written was his apologia, "Seven Defensiones" (1538), followed by a pamphlet, "The Doctor's Labyrinth," which Pachter regards as the most readable of all his writings. Finally reaching Salzburg, where the Prince Bishop had offered him asylum, Paracelsus wrote his will and 3 days later died. The epitaph which he composed is given, echoing some of the old bombast and, strange if true, including the exact date of his death. Characteristically, the cause of his death is uncertain, opinions varying from an overdose of his elixir of life to wounds received in a tavern brawl.

The printing press has been liberal to Palthenius in 1605, for over 3 centuries retreatises printed during his lifetime, Huser's "Die Bücher und Schrifften . . . des Paracelsi" (in 10—here given as 12—volumes) appeared before the end of the century. This and an 11-volume Latin edition, prepared by Palthenius in 1605, for over 3 centuries remained the standard editions. In 1922-33, Sudhoff, who claimed kinship with Paracelsus, prepared a *Sämtliche Werke* with copious annotations, in 14 volumes. Unfortunately he did not live to complete the second part (theological and philosophic), which is now in the hands of his co-editor, W. Matthiessen. To these and numerous smaller productions, Dr. Pachter's work is a useful addition, both because very few publications have been written in English and on account of his novel emphases and fresh points of view.

E. K.

THE ORIGINS OF MODERN SCIENCE 1300-1800. By H. BUTTERFIELD, M.A., Prof. of Mod. History in the Univ. of Cambridge. Pp. 270; no ills. London: G. Bell and Sons, 1950. Price, $2.50.

IN these lectures, given at the University of Cambridge in 1948, this general historian chiefly concerns himself with "the scientific revolution" which he traces back in a continuous line well beyond the usually accepted 16th & 17th centuries to the Parisian nominalists of the late medieval 14th century. As the revolution overturned the science of both the ancient and Middle Ages, he maintains that "it outshines everything since the rise of Christianity", reducing the Renaissance and the Reformation to the level of mere episodes.

Obviously, in a presentation of this size, a complete coverage of origins spread over five centuries—and still continuing for that matter—is out of the question. The author has wisely chosen to concentrate, in the twelve chapters, on pivotal moments in the lines of strategic change, especially where the solution of problems required a change in the discoverer's mentality. Copernicus, Harvey, Galileo, Kepler, Bacon, Descartes, Newton, and Boyle are the chief actors selected from the fields of astronomy, mathematics, physics

and biology to be viewed in relation to the cultural progress of the Western World. Incidental digressions on the reader's need for knowledge of the past to understand what the pioneer is attacking, the necessity for the scientist constantly to overhaul concepts which prove to be inadequate, and for the reader to avoid the trap of attributing undue significance to early statements because viewed in the light of modern knowledge, are found spread through the book. Such lively phrases as "Bruno . . . that *enfant terrible* amongst the 16th century Italian speculators", and bold estimates such as that the grand synthesis of Newton's "*Principia* "represented the culmination of the scientific revolution and established the basis of modern science" add to the reader's pleasure and profit derived from this admirable work.

The author did not need to apologize in the Introduction for invading the history of science; the text reveals his thorough familiarity with his subject while his treatment of it, presented in an easy, pleasant style, produces a desirable result for both historian and scientist. It would seem, too, an ideal book for use in a course in collegiate General Education. E. K.

THE HEALING TOUCH. By HARLEY WILLIAMS, author of Doctors Differ and other works. Pp. 370; ills. Springfield, Ill.: C. C Thomas, 1951. Price, $6.75.

THIS book is more a gallery of medical portraits than a collection of bits of medical history, though it gives a good picture of the times as well as of the personalities covered. It is really a second edition and, unusual for later editions, is shorter than the first by some 40 pages. The only indication that there was a first (published by Pace in England in 1949) is found in the copyright statement.

One quickly falls under the spell of the author's engaging style. Of the 3 Royal Physicians observed in Book 1, Sir Wm. Knighton and Sir James Clark, though inconspicuous historically, are with us as live persons and give, too, a good idea of the life of the people and the state of early 19th century medical practice. Chadwick and Southwood Smith, the subjects of Book 2, are fortunately the most skillfully handled of any in the whole work, as sanitation, drains, Boards of Health and the like are without interest for the average reader. Florence Nightingale and Octavia Hill (Book 3) are portrayed vividly, as indeed are all the heroes of this study; but, to this reviewer, with too much suppression of the frailties of the Lady of the Lamp. In the next chapter the author's colorful imaginative style finds full play in the life of Brown-Sequard, the "Ulysses of Biology", the "Balzac of Science", the "Father of Endocrinology" who, using himself as a test animal, so exaggerated the vitalizing effects of testicular extracts, that they came under "the taboo of respectability" until years after most of the glands of internal secretion were well established. Brown-Sequard's experiments would not pass muster today, but in Mr. William's opinion they constitute one of the cornerstones of modern medicine, nevertheless.

In the 94 pages of Book V, the longest in the volume, the underlying phenomena of the New World of Medicine are explored. The growth of the Mayo Clinic, which, as a wag put it, "made Chicago into a stopping place between New York and Rochester", serves as an illustration of two of the most significant developments—organization of the doctor's scientific work, and the idea of group medicine. Together with the 3 Mayos, father and sons, a dozen others are selected to exemplify the truly great modern achievements, with due appreciation of the limitations of physical treatment of disease, and the need for the art of healing.

Never has the reviewer read a medical book with greater ease and pleasure E. K.

OBSTETRICAL PRACTICE. By ALFRED C. BECK, M.D., Prof. Emeritus of Obstetrics and Gynecology, State University of New York College of Medicine, New York, N. Y. 5th ed. Pp. 1073; 969 ills. Baltimore: Williams & Wilkins Co., 1951. Price, $10.00.

SINCE the previous revision of Beck's "Obstetrical Practice" appeared in 1947, considerable alteration was required to bring the fifth edition up-to-date. Changes are obvious throughout the text and include the most recent ideas on maternal, fetal and placental physiology, the management of normal and abnormal labor and the management of other obstetric complications.

In line with the current thoughts regarding pelvimetry the external measurements are only mentioned, emphasis being placed on internal manual evaluation and Roentgen pelvimetry. Rh iso-immunization, vascular complications and other medical conditions are thoroughly discussed. Many of the illustrations have been redone and, as in other editions, are clear and concise, adequately illustrating the material in the text.

This book is highly practical for the use of both students and practitioners because of its

concentration on fundamental obstetric principles, its explicit directions for the management of obstetric conditions and its clear illustrations. J. W.

ROENTGEN EXAMINATIONS IN ACUTE ABDOMINAL DISEASES. By J. FRIMANN-DAHL, M.D., Ph.D., Chief of Roentgen Department, Ulleral Hospital, Oslo, Norway. Pp. 323; 305 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $10.50.

THIS is a valuable book, being a comprehensive work of the Roentgen aspects of acute abdominal diseases. The author has recognized the need for a book of this sort, noting that acute abdominal diseases are among the most frequent and among the most difficult conditions to diagnose in the hospital. The decided drop in death rate of bowel obstruction is attributed, in large part, to correct and early diagnosis.

The book is valuable because of its detail in utilizing all Roentgen aids; for example, the examination of the flanks, the use of various positions of the patient, et cetera. The book serves as a ready reference for such conditions as mechanical obstructions of the small and large bowel, intussusception, volvulus, paralytic ileus, rupture of abdominal viscera, et cetera. H. W.

PHASE MICROSCOPY, PRINCIPLES AND APPLICATIONS. By ALVA H. BENNETT, HELEN JUPNIK, HAROLD OSTERBERG, and OSCAR W. RICHARDS. Research Laboratory, American Optical Company, Stamford, Connecticut. Pp. 320; 91 ills. New York: John Wiley & Sons, Inc. 1951. Price, $7.50.

THIS book presents a working knowledge of the highly useful method of phase microscopy. It is written by four qualified scientists, each of whom has made outstanding contributions in this field.

The theory of phase microscopy is developed in a simplified discussion and is applied to the best choice of a diffraction plate suited to given object conditions. Chapters on instrumentation, principles of color phase contrast, and on applications and techniques of the phase procedure are well covered. In the appendix is a mathematical treatment of the diffraction theory of phase microscopy with Köhler illumination.

This practical book contains the material the microscopist needs in order to apply this method advantageously to a wide variety of technical and scientific problems. G. H.

CLINICAL PATHOLOGY OF THE EYE. By BERNARD SAMUELS, M.D., Emeritus Clinical Professor of Ophthalmology, Cornell University, and ADALBERT FUCHS, M.D., E. O. Professor of Ophthalmology, University of Vienna, Consulting Ophthalmologist, New York Eye & Ear Infirmary. Pp. 408; 418 ills. New York: Paul B. Hoeber, Inc., 1952. Price, $20.00.

THIS beautifully and profusely illustrated textbook fulfills a long standing need in teaching the essential fundamentals of ophthalmic pathology. It is written by authorities in the field, and it is regrettable that it did not appear twenty years ago.

The authors have avoided the use of excess verbiage and have been wise in omitting many of the less important subjects.

The collections of illustrations are exceptionally good, but it is regretted that the eosin stain is more predominant than that which is routinely used by others.

The authors have, in many instances, held to terminology which other pathologists are endeavoring to eradicate, such as albuminuric retinitis, glioma of the retina, and sarcoma of the choroid.

The book is worth the price and should be included in the library of all who are sincerely interested in the eye. G. G.

NEW BOOKS

Physical Medicine and Rehabilitation for the Aged. By WALTER S. MCCLELLAN, M.D., Med. Director, Saratoga Spa, Saratoga Springs, N. Y.; Assoc. Prof. Med., Albany Med. Coll. Amer. Lecture Series, No. 105. Pp. 81; 9 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.00.

Cardiac Pain. By SEYMOUR H. RINZLER, M.D., Adjunct in Med. and Cardiovascular Research Unit, Beth Israel Hosp., N. Y. Pp. 138; 9 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $3.75.